Diffusion Abnormalities in Parkinson's disease depend on clinical subtype

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Purpose

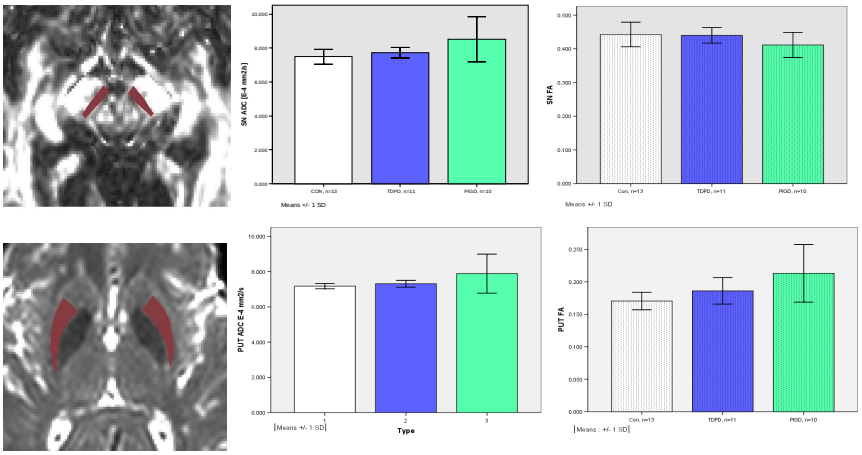
Parkinson's disease (PD) is characterised pathologically by progressive neuronal loss associated with the presence of Lewy bodies in a number of subcortical nuclei. Substantial loss of dopaminergic neurones in the substantia nigra pars compacta is associated with the development of motor symptoms including tremor and akinetic-rigidity. Clinical diagnosis has been improved by standardised criteria, but remains challenging in non specialist centres and during the early disease stage.[1] A non-invasive diagnostic biomarker would be helpful to assist early diagnosis and evaluation of neuroprotective trials.[2] Standard MRI is insensitive to the pathology of IPD, and even the anatomic delineation of the substantia nigra is controversial. A number of MRI sequences (inversion MRI, iron sensitive) have been tested with variable success in detecting nigral pathology in PD brains. Diffusion MRI has been successfully used to assess ultrastructural pathology associated with a number of other neurodegenerative diseases including atypical parkinsonism. Surprisingly few studies have looked at the diagnostic value of diffusion measurements in the substantia nigra as a biomarker of IPD. Moreover, the clinical heterogeneity of PD has been largely ignored. There are two main clinical subtypes, the tremor dominant (TDPD) and the postural instability gait disorder (PIGD) type with the latter showing a worse prognosis.[3]
We aimed to characterise nigral pathology in Parkinson disease using high resolution diffusion tensor imaging at 3 Tesla and to investigate differences between major clinical subtypes.

Method

The study was approved by the local Ethics Committee. 35 subjects (14 healthy volunteers [60.8 ± 12.8], 21 PD patients, 10 PIGD [64.9 ± 11.4], 11 TDPD [63.4 ± 15.3]) were included. All subjects were cognitively tested using the Addenbrooke's Cognitive Examination battery[4]. Clinical severity was assessed in patients using the Unified Parkinson disease rating scale (UPDRS).[5] Duration, type and dose of L-DOPA and dopaminergic medication was recorded. Diffusion tensor imaging was performed at 3 T (Philips Achieva, b=0 (3 averages) and b= 1000 [32 gradient directions], SENSE factor 2, TR/TE 11692/60ms, 52 slices 2 mm thick with 2x2mm2 acquisition voxel size reconstructed as 2x1x1mm3). Data processing was done offline using FSL software for ADC and FA calculation. Region of interests were manually drawn on three consecutive slices (Fig) in the substantia nigra (SN centred on the pars compacta), and putamen (PUT) using JIM software. Mean values were averaged for bilateral SN and PUT excluding CSF containing pixels by using a cut-off of ADC >1.8 x10-3mm 2/s. No CSF correction was done for FA values. ANOVA was used for between group comparison of clinico-epidemiologic data. Non parametric tests were used for group comparison and correlation analysis of diffusion metrics. No multiple test correction was performed.

Results

One control with poor cognitive performance (ADB 75) was excluded. There were no differences in age or cognitive status between groups. PD patients showed significantly elevated ADC in SN (0.810 ± 0.10 vs.0.748 ± 0.045 $x10^{-3}mm^2/s$, p=0.02), and moderately elevated ADC in PUT (0.759 ± 0.081 vs.0.718 ± 0.015 $x10^{-3}mm^2/s$, p=0.046). Putamenal FA was signficantly elevated in patients (0.199 ± 0.036 vs.0.170 ± 0.013, p=0.003).
Stratifying patients into TDPD and PIGD revealed significantly higher SN ADC in PIGD (Fig upper row, middle). PIGD differed from controls due to higher SN ADC and PUT FA, whereas TDPD showed only higher PUT FA compared with controls (lower row, right).



Age was significantly positively related to PUT ADC (r=0.516), and SN ADC (r=0.446) and FA PUT (r=0.383). Cognitive performance was negatively correlated with SN ADC (r= -0.407 [ACE]).
Disease severity was positively associated with PUT ADC (r=0.494) and negatively with SN FA (r=-0.444). L-DOPA dose was strongly negatively associated with PUT FA (r=-0.816).

Figure:
Regional diffusion metrics in controls, TDPD and PIGD
Upper row: Substantia nigra, pars compacta, lower row: putamen. Left: ROI, middle: group mean+/-SD for ADC, right: for FA). White: controls, blue: TDPD, green:PIGD.

Discussion

This study is the first to demonstrate increased diffusivity in the substantia nigra in PD brains as a potential marker of the underlying neurodegenerative process. The finding of more pronounced diffusion facilitation in PIGD concords well with the poorer prognosis seen in PIGD patients. Similar to a previous study[5] we found mildly reduced SN FA that failed to reach significance in our smaller cohort, but we found a significant inverse correlation with clinical severity assessed by UPDRS. Interestingly, we also found putamenal diffusion abnormalities in PD that were more pronounced in PIGD and associated with clinical severity. Elevated PUT ADC may reflect extranigral neurodegeneration or additional microscopic vascular disease. The finding of elevated PUT FA with a strong association with L-DOPA dose was unexpected and is difficult to explain in the context of neurodegeneration, which typically is characterised by elevated ADC and reduced FA. Putamenal grey matter loss perceivably may lead to FA elevation. The study is limited by its sample size and lack of CSF correction for FA values that may have biased putamenal FA.

Conclusion

Diffusion abnormalities were seen in PD brains that may reflect neuronal cell loss and tissue destruction and hence may serve as biomarker of the underlying neurodegenerative process. Nigral ADC elevation was selectively noted in patients with postural instability gait disorder providing further evidence for a biological differences underlying the heterogenous clinical phenotypes. Further studies are needed to assess the diagnostic accuracy of nigral ADC in larger patient groups and whether it can reflect disease progression.

References

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