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Fractional Anisotropy and Apparent Diffusion Coefficient values on Diffusor Tensor Imaging in Parkinson's Disease: A case-control study

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Abstract

Introduction: Recent evidence is shedding insights into the functional alterations in the sensorimotor, visual and basal ganglia networks in Parkinson's Disease (PD) patients. We evaluated the Functional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) values in PD patients with DTI using Region of Interest (ROI) basis and compare it with healthy controls.

Methodology: A case control study was conducted comprising of 40 PD patients, and similar healthy controls. They were evaluated using 1.5 tesla MRI Machine and DTI were performed using a single-shot sequence with diffusion encoding in 31 directions. In each subject, four deep grey matter structures (Caudate nucleus, putamen, pallidum and substantia nigra) were segmented. Differences in FA and ADC between groups were assessed using t-test to compare means.

Results: Mean FA values of PD cases when compared with control cases were significantly less on both sides. Mean ADC values of PD cases were significantly higher as compared to controls at caudate nucleus and substantia nigra on both sides. Mean ADC values for lentiform nucleus were not significantly different between PD cases and controls on both sides. ROC analysis found the cut off value of FA and ADC to be 0.26 and 8.05 at caudate nucleus, 0.26 and 7.5 at lentiform nucleus and 0.46 and 8.2 at substantia nigra respectively.

Conclusions: Advanced image analysis is derived from improved image algorithms, which can help in automated differentiation of PD and related disorders. DTI is a promising tool to assess PD-related neurodegeneration and potentially could serve as marker for PD.

Keywords: Parkinson's disease; Diffusion weighted imaging; Magnetic resonance imaging; Fractional anisotropy.

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Introduction

Recent advances in neuroimaging methods have made it possible to investigate the anatomical microstructures and the impact of altered pathophysiological mechanisms on brain functioning. In vivo assessments, white matter integrity has been made possible with the current Magnetic Resonance Imaging (MRI) technology by means of diffusion-tensor (DT) imaging. This technique directly measures several unique aspects of bulk tissue microstructure by mapping water proton motion within the tissue microenvironment and express themselves in terms of fractional anisotropy (FA) and Apparent Diffusion Coefficient (ADC).[1] Reduced FA and increased ADC values are associated with underlying histopathological processes such as gliosis, demyelination, edema and axonal loss.[2] Accumulating evidence is shedding insights into the functional alterations in Parkinson's Disease (PD), particularly in the sensorimotor, visual and basal ganglia networks.

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Hence, we aimed to evaluate the FA and ADC values in caudate nucleus, globus pallidus, putamen and substantia nigra in PD patients with DTI using Region of Interest (ROI) basis and compare it with healthy controls.

Materials and Methods

Study Design and Setting

A case control single institutional study was conducted in the departments of Radio-diagnosis and Neurology of Dr. Rajendra Prasad Government Medical College (RPGMC), Kangra at Tanda, Himachal Pradesh. The study comprised of 40 PD patients, who were initially evaluated in the Department of Neurology with clinical history of Parkinson's disease and then referred to the department of Radio-diagnosis for MRI of brain and similar number of healthy controls.

Sample population

The sample size was calculated using random sampling of case control study with expected prevalence of PD in sub Himalayan region of 14.1 % in previous study by Razdan *et al.*[3] in 1994. By using the formula, we calculated the sample size 73 with precision of ±0.08. So, we included 80 subjects including 40 PD patients and 40 controls. We included all patients diagnosed with Parkinson's disease (MDS clinical diagnostic criteria for Parkinson's disease)[4] with other Parkinson's-plus syndromes, with or without ongoing treatment for Parkinson's disease. We excluded patients who had contraindication to MRI, with neurological comorbidities, had neurosurgical procedures and suffered from traumatic brain injury and non-consenting patients.

MR acquisition

The patients and control cases were evaluated in the department of Radio-diagnosis using 1.5 tesla MRI Machine (Signa Excite, Brain HR 8 coiled, and GE Healthcare) with a standard quadrature head coil. DTI was performed using a single-shot EPI sequence with diffusion encoding in 31 directions (b values 0 and 1000 s/mm^2). DTI acquisition-38 slices, thickness = 3 mm with no spacing, repetition time = 10600 ms, echo time = 93.6 ms, number of excitations = 1, frequency = 128, phase FOV = 1, voxel: 3 × 3 × 3 mm. The reconstructed voxel size was 49,152 mm^3, and 38 slices were acquired. Data Processing and Fibre Tracking was done by using software FSL. In each subject, four deep grey matter structures (Caudate nucleus, putamen, pallidum and substantia nigra) were segmented. Value of FA and ADC were obtained by using ROI based analysis. Subsequently, ROIs were used to measure the FA and ADC in gray matter nuclei. Superimposition of 3d FSPGR sequences was applied to get accurate level. A single operator took the images that was blinded to clinical profile of the patients.

Data Collection and Data Analysis

Data were collected using a pre-designed semi-structured proforma. Baseline characteristics and clinical information of the patients and controls were described as frequency distribution. Differences in FA and ADC between groups were assessed using t-test to compare means. Receiver Operating Characteristic (ROC) analyses were done to measure cut-off values for FA and ADC at different ROI in the PD patients.

Results

The patients' age ranged from 24 years to 85 years with mean age of 59.10 ± 10.33 SD years while in control group, age ranged from 26 years to 83 years with mean age of 49.77 ± 13.03 SD years (Table 1). Mean age of presentation in PD female patients were 60 years and in male patient was 58 years. Thirty-one (77.5%) patients were in age group of 51–70 years. We had equal number of male and female patients and in controls 18 males and 22 females

Table 1: Baseline characteristics of the PD patients and controls included in the study

Variable	PD patients (n=40)		Controls (n=40)	
	n	%	N	%
Age distribution (in years)				
21 to 40	1	2.5	9	22.5
41 to 60	22	55	22	55
61 to 80	16	40	9	22.5
More than 80	1	2.5	0	0

Variable	PD patients (n=40)		Controls (n=40)	
	n	%	N	%
Gender distribution				
Females	20	50	18	45
Males	20	50	22	55
Smoking				
Yes	18	45	19	47.5
No	22	55	21	52.5
Alcohol				
Yes	18	45	17	42.5
No	22	55	23	57.5
Chief complaints				
Tremors	20	50	–	–
Difficulty walking	4	10	–	–
Ataxia	2	5	–	–
Slowness of movement	2	5	–	–
Weakness	1	2.5	–	–
Unable to speak	1	2.5	–	–
Seizure	1	2.5	–	–
Family history of PD				
Yes	1	2.5	–	–
No	39	97.5	–	–
Taking treatment for PD				
Yes	32	80	–	–
No	8	20	–	–

were taken. Smoking and alcohol consumption was equally distributed among PD patients and controls. Tremors were the commonest symptoms, which was found in 20 (50%) patients, abnormal body movements in 9 (22.5%), difficulty in walking in 4 (10%), ataxia and slowness of movements in 2 (5%) patients each, weakness, seizures and inability to speak constituted the major complaint 1 (2.5%) case each in our study. There were more than two symptoms in few patients. Only one patient had a family history of PD, which may suggest that PD is a non-familial disease. Thirty-two (80%) of the patients were on anti-Parkinson's medication at the time of MRI evaluation. Duration of treatment ranged from 1 to 48 months with average duration of 11.43 months.

Table 2 describes the clinical findings of the patients included in the study. Tremors and abnormal movements were most common coexisting complaints in 37 (92.5%) patients.

Table 2: Clinical examination findings of the PD patients (n=40) included in the study

Clinical examination findings	n	%
Gait		
Abnormal	29	72.5
Normal	11	27.5
Cognitive impairment		
Yes	16	40
No	24	60
Facial expression		
Abnormal	5	12.5
Normal	25	62.5
Tremors		
Yes	35	87.5
No	5	12.5

Clinical examination findings	n	%
Rigidity		
Yes	13	32.5
No	27	67.5
Posture		
Abnormal	20	50
Normal	20	50
Posture instability		
Yes	29	72.5
No	11	27.5

Table 3 describes the FA and ADC values at bilateral caudate nucleus, lentiform nucleus (putamen and globus pallidus) and substantia nigra by using ROI based analysis in PD patients and controls. Mean FA values of PD cases when compared with control cases were significantly less on both sides. Mean ADC values of PD cases were significantly higher as compared to controls at caudate nucleus and substantia nigra on both sides. Mean ADC values for lentiform nucleus were not significantly different between PD cases and controls on both sides. ROC analysis measured the cut-off values for FA and ADC at different regions of interest along with their operating characteristics (Table 4).

Table 3: Comparing Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) values of Parkinson's disease patients with controls

Region of interest	PD	Controls	*p*-value	PD	Controls	*p*-value
	Right side			Left side		
Mean Fractional Anisotropy						
Caudate nucleus	0.2201 ± 0.04212	0.2872 ± 0.08691	<0.001	0.21811 ± 0.0411	0.2878 ± 0.07916	<0.001
Lentiform nucleus	0.2279 ± 0.04994	0.2942 ± 0.07959	<0.001	0.2342 ± 0.07155	0.2971 ± 0.07455	<0.001
Substantia Nigra	0.3946 ± 0.56704	0.4418 ± 0.06881	<0.01	0.3993 ± 0.05403	0.4457 ± 0.06679	<0.01
Apparent Diffusion Coefficient (10^{-4} mm^2/sec)						
Caudate nucleus	9.0178 ± 1.44272	8.0828 ± 0.86136	<0.01	8.8490 ± 1.62023	8.0503 ± 0.86136	<0.01
Lentiform nucleus	8.0188 ± 0.88354	7.8268 ± 0.49005	0.23	7.9863 ± 0.76136	7.7713 ± 0.50604	0.14
Substantia Nigra	8.8078 ± 1.19564	7.7783 ± 1.23974	<0.001	8.4918 ± 1.33124	7.7015 ± 1.20718	<0.01

Table 4: ROC analysis showing operating characteristics differentiating between PD patients and controls at different anatomical locations

Region of interest	DTI measure	Cut-off	Sensitivity	Specificity	PPV	NPV
Caudate nucleus	FA	0.26	95%	55%	74%	81.25%
	ADC × 10^{-4} mm^2/sec	8.05	75%	60%	56.56%	73.72%
Lentiform nucleus	FA	0.265	90%	83.75%	51.79%	89.33%
	ADC × 10^{-4} mm^2/sec	7.505	67.50%	30.50%	71.70%	47.82%
Substantia nigra	FA	0.462	87.25%	52.50%	52.40%	64.47%
	ADC × 10^{-4} mm^2/sec	8.025	73.75%	75%	50.42%	73.40%

Discussion

DTI helps us in assessing the structure of cerebral tissue by estimate changes in the integrity of white matter.[5] DTI measures "the random motion of water molecules in fluid water", which is specifically useful to assess neural fibres.[6] ADC refers to the diffusion of water molecules in organic tissues, and increased ADC suggests degeneration of the tissue.[7] FA characterizes the orientation distribution of the

random movement of water molecules; value closer to 0 suggests damaged tissue when measured in white matter.[8] In our study, mean FA values of PD cases when compared with control cases were significantly less on both sides at caudate nucleus, lentiform nucleus and substantia nigra. Our findings are similar to other publications claiming very high diagnostic accuracy,[9] but also unlike others which showed small or no PD induced nigral FA decrease.[10] In fact, Wang *et al*. even reported an increase of nigral FA in PD patients and concluded that traditional DT imaging indexes, including FA, have limited value in the diagnosis of PD[11] A meta-analysis by Schwarz *et al*. revealed a significant reduction in strial FA (weighted pooled disease effect size of−0.9, p<0.0001), however, the variation among the included studies was very high (I_2 = 86%).[12] Another meta-analysis by Cochrane and Ebmeier found similar highly significant PD induced nigral FA reduction.[13] Another reason for the large variability of the values of FA is the reason that iron deposition in the basal ganglia, specifically in the Substantia nigra increases with age.[14] Iron deposition is accelerated in PD patients[15] and may be associated with disease severity and duration as well. This deposition of iron may alter the FA values and decrease observable differences when comparing PD patients and controls.

Regional increases in diffusivity metrics like ADC are useful markers of neurodegeneration that can help to distinguish the different variants of Parkinsonian syndrome from PD.[16] We found the mean ADC values of PD cases to be significantly higher as compared to controls at caudate nucleus and substantia nigra on both sides. However, mean ADC values for lentiform nucleus were not significantly different between PD cases and controls on both sides. Chan *et al.* assessed ADC values of 73 PD cases and 78 health controls but could not find a significant difference.[17] Rizzo and colleagues assessed ADC values in several ROIs at 1.5T in PSP, PD and health controls.[18] They found significantly higher ADC values in PSP and CBS compared to PD patients in the putamen and found SCP and putaminal ADC to be the best predictor for differentiating between PD, Parkinsonian syndromes and health controls.

Our ROC analysis shows that FA values are 90% sensitive and 84% specific in lentiform nucleus for the diagnosis of PD, while the sensitivity and specificity were lower in substantia nigra (87.25% and 52.5% respectively). FA was highly sensitive parameter with sensitivity of 95% to detect the changes in caudate nucleus but was least specific (55%). Sensitivity and specificity for ADC was 75% and 60% in the caudate nucleus, 67.5% and 30% in the lentiform nucleus and 73.75% and 75% in the substantia nigra. Peran *et al.* compared thirty PD cases and 22 health controls and found that a combination of volumetry, mean relaxation rates, mean diffusivity and FA applied in 6 deep grey matter structures (SN, red nucleus, thalamus, putamen, caudate, pallidum) achieved a maximum AUC of 0.99.[19] Hirata and colleagues in their meta-analysis analysed data of 806 PD patients and 626 controls from 22 studies and found decreased nigral FA values had a pooled sensitivity of 72% and specificity of 63%.[20] Better discrimination could be achieved when nigral FA, was combined with other quantitative MR parameters sensitive to complementary tissue characteristics (i.e. multimodal MRI). Prodoehl *et al.* applied a multi-target DTI approach using different DTI metrics (FA, radial diffusivity, longitudinal diffusivity, and mean diffusivity) focused on the basal ganglia and cerebellum in 15 patients with PD and 12 patients with essential tremors and found that DTI measures from the caudate and substantia nigra separated PD from essential tremor with a sensitivity of 92% and a specificity of 87%.[21]

Conclusion

An emerging field in image analysis is derived from advances in image analysis algorithms, and this has led to the development of automated differentiation of PD and related disorders. Ours is one of the few DTI analysis studies which have been done on Indian PD patients and our results should be confirmed by further large-scaled multi-centric studies. Our results suggest that DTI is a promising tool to assess PD-related neurodegeneration and potentially could serve as a marker for PD.

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References

1. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B. 1996;111(3):209–219.
2. Chan LL, Ng KM, Rumpel H, *et al.* Transcallosal diffusion tensor abnormalities in predominant gait disorder Parkinsonism. Parkinsonism and Related Disorders. 2014;20:53–9.

3. Razdan S, Kaul RL, Motta A, *et al.* Prevalence and pattern of major neurological disorders in rural Kashmir (India) in 1986. Neuroepidemiology. 1994;13:113–19.
4. Ronald B, Daniela P, Stern M, *et al*. MDS clinical diagnostic criteria for Parkinson's disease. Wiley Online Library 2015;30:15.
5. Conturo TE, Lori NF, Cull TS, *et al.* Tracking neuronal fiber pathways in the living human brain. Proc. Natl. Acad. Sci. U.S.A. 1999;96(18):10422–27.
6. Stieltjes B, Brunner RM, Fritzsche KH, *et al.* Diffusion Tensor Imaging. Springer Berlin Heidelberg, Berlin, Heidelberg. 2012.
7. Syková E. Extrasynaptic volume transmission and diffusion parameters of the extracellular space. Neuroscience 2004;129(4):861–76.
8. Schulte T, Sullivan EV, Müller-Oehring EM, *et al.* Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. Cereb. Cortex 2005;15(9):1384–92.
9. Vaillancourt DE, Spraker MB, Prodoehl J, *et al.* High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. Neurology. 2009;72:1378–84
10. Menke RA, Jbabdi S, Miller KL,*et al.* Connectivity-based segmentation of the substantia nigra in human and its implications in Parkinson's disease. Neuro Image. 2010;52:1175–1180.
11. Wang JJ, Lin WY, Lu CS, *et al.* Parkinson disease: diagnostic utility of diffusion kurtosis imaging. Radiology. 2011;261:210–217.
12. Schwarz ST, Abaei M, Gontu V, *et al.* Diffusion tensor imaging of nigral degeneration in Parkinson's disease: a region-of-interest and voxel-based study at 3 T and systematic review with meta-analysis. NeuroImage: Clinical. 2013 Jan 1;3:481–8.
13. Cochrane CJ, Ebmeier KP. Diffusion tensor imaging in parkinsonian syndromes: a systematic review and meta-analysis. Neurology. 2013;80:857–64.
14. Daugherty A, Raz N. Age-related differences in iron content of subcortical nuclei observed in vivo: a meta-analysis. NeuroImage. 2013;70:113–21.
15. Lotfipour AK, Wharton S, Schwarz ST, *et al.* High resolution magnetic susceptibility mapping of the substantia nigra in Parkinson's disease. J. Magn. Reson. Imaging. 2012;35:48–55.
16. Blain CRV, Barker GJ, Jarosz JM, *et al.* Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. Neurology. 2006;67, 2199–2205.
17. Chan LL, Rumpel H, Yap K, *et al*. Case control study of diffusion tensor imaging in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78:1383–6.
18. Rizzo G, Martinelli P, Manners D, *et al*. Diffusion-weighted brain imaging study of patients with clinical diagnosis of corticobasal degeneration, progressive supranuclear palsy and Parkinson's dis-ease. Brain. 2008;131:2690–700.
19. Peran P, Cherubini A, Assogna F, *et al*. Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. Brain J Neurol. 2010;133(11):3423–33
20. Hirata FC, Sato JR, Vieira G, *et al*. Substantia nigra fractional anisotropy is not a diagnostic biomarker of Parkinson's disease: a diagnostic performance study and meta-analysis. Eur Radiol. 2017 Jun;27(6):2640-48.
21. Prodoehl J, Li H, Planetta PJ. Diffusion tensor imaging of Parkinson's disease, atypical parkinsonism, and essential tremor. Mov Disord Off J Mov Disord Soc. 2013;28(13):1816–1822