CLINICAL PROFILE AND DIFFUSION TENSOR IMAGING IN PARKINSONIAN SYNDROMES

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ABSTRACT

BACKGROUND

Advances in MRI techniques have provided new tools for the diagnosis of PD in its early stages and have discriminated it from other atypical PD syndromes.

Aims and Objectives- To study the clinical profile and neuroimaging aspects of patients presenting with parkinsonian symptoms and aiding in their diagnosis and management. To explore the role of DTI in early diagnosis and its utility as a potential screening tool for parkinsonian syndromes.

MATERIALS AND METHODS

50 patients aged above 18 yrs. presenting with primary parkinsonism, parkinsonism plus syndromes, predominant parkinsonism features in heredodegenerative parkinsonism groups were included. Patients were subjected to detailed case proforma questionnaires and categorized under two groups typical and atypical parkinsonism. Clinical assessment was done by Unified Parkinson's Disease Rating Scale (UPDRS), Modified Hoehn and Yahr staging and a 750 wide bore 3 Tesla GE-made MRI with Echo planar and diffusion weighted imaging in 25 directions was used for imaging of the brain. In the present study, 25 patients and 10 controls in whom DTI was performed, fractional anisotropy (FA) values were obtained from regions of interest (ROI)- cingulate cortex, basal ganglia, corticospinal tracts, superior longitudinal fasciculus, substantia nigra, thalamus regions of brain.

RESULTS

In our study, male population represented higher cases than females and mean age of presentation was 49.94 yrs. Typical PD patients constituted 84% and atypical PD 16%. Median UPDRS- III motor scale for typical PD patients was 36 and atypical PD patients was 55. The mean FA values of substantia nigra regions of PD patients when compared to controls, was lower but statistically not significant (0.4256 vs 0.44801, p=0.076). None of the FA values in studied regions showed statistically significant difference between patients and controls.

CONCLUSION

Our study DTI findings using ROI analysis helped in differentiating typical vs atypical PD syndromes and also diagnosing PD patients at an early stage. Even though there was no statistical significance among core parameters obtained, this study reinforces the findings in terms of trends in FA values thereby establishing the role of DTI in diagnosing PD patients.

KEYWORDS

Diffusion, Tensor Imaging, Parkinsonism.

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BACKGROUND

Parkinsonism includes idiopathic Parkinson's disease, atypical parkinsonism, heredodegenerative and secondary parkinsonism. Idiopathic Parkinson's disease usually occupies more than 75% of parkinsonism spectra. Parkinson plus syndromes or atypical parkinsonism include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB) and parkinsonism-dementia-amyotrophic lateral sclerosis complex. Secondary parkinsonism is due to multiple causes such as brain injury, encephalitis, meningitis, stroke, Wilson disease, carbon monoxide poisoning, mercury poisoning, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), narcotic overdose, drug induced (antipsychotic drugs, anaesthetic drugs, prokinetic drugs) and HIV (human immunodeficiency virus) infection.[1] The diagnosis of PD is clinical and confirmation is possible only post mortem. Early accurate clinical diagnosis of PD may be important for institution of disease course – modifying treatments for prognostication.[2]

For a clinician it is difficult to discriminate atypical PD syndromes from idiopathic PD in their initial stages. To date, up to 20% of the cases thought to be idiopathic PD turned out to be other diseases, despite strict diagnostic criteria being used.

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Advances in MRI and functional imaging have provided new tools for the diagnosis of PD in its early stages and have discriminated it from other atypical PD syndromes.[3] Diffusion tensor imaging (DTI) is an MRI technique assessing the orientation and integrity of white matter tracts in vivo by measuring the diffusion of water molecules in neural fibers and it also shows promise for studying gray matter areas.[4]

The present study is undertaken to assess the clinical profile in parkinsonism patients and its correlation with neuroimaging particularly diffusion tensor imaging.

Aims and Objectives

- To study the clinical profile of patients presenting with parkinsonian symptoms.
- To study the role of neuroimaging in understanding parkinsonian syndromes and aiding in their diagnosis and management.
- To explore the role of DTI in early diagnosis and its utility as a potential screening tool for parkinsonian syndromes.

MATERIALS AND METHODS

Study Design

Prospective study.

Study Period

March 2014- December 2015.

Study Subjects

The present study was done in the department of Neurology, Andhra Medical College, King George Hospital, Vishakhapatnam.

50 patients who presented to the Neurology OPD and wards with features of primary parkinsonism and parkinsonism –plus syndromes were recruited into the study.

Inclusion Criteria

All patients aged above 18yrs presenting to OPD and wards of Neurology department, KGH with primary parkinsonism, parkinsonism plus syndromes, predominant parkinsonism features in heredodegenerative parkinsonism groups will be included in the study.

Exclusion Criteria

All patients presenting with non-parkinsonian symptoms in heredodegenerative parkinsonism group, secondary parkinsonism-acquired from infections, drugs, toxins, vascular, trauma and thyroid related disorders were excluded from the study.

Study Tools

1. UKPDS brain bank criteria for idiopathic Parkinson's disease.
2. NINDS-SPSP criteria for progressive supra nuclear palsy.
3. European consensus criteria for multiple system atrophy
4. Unified Parkinson's disease rating scale – Part-I,II,III
5. Modified Hoehn and Yahr staging for idiopathic Parkinson's disease.

Study Procedures

Patients fulfilling inclusion exclusion criteria were subjected to detailed case proforma questionnaires followed by UPDRS scoring, Modified Hoehn and Yahr staging and later MRI including DTI was done.

MRI

750 wide bore 3Tesla GE made model with Echo planar and diffusion weighted imaging in 25 directions was used.

DTI Analysis

FA values were obtained from various brain structures on the DTI scan. The structures studied were: caudate, putamen, globus pallidus, thalamus and substantia nigra. Regions of interest (ROIs) of size 40 mm3 were drawn in the substantia nigra, which was found between the red nucleus and the crural fibres of the cerebral peduncle at the same level in all subjects. ROIs were drawn in the caudate (120 mm3), putamen (230 mm3) and globus pallidus (86 mm3) on the section one slice above the anterior commissure, and in the thalamus (689 mm3) on the next superior section. The radiologist and the technician were blinded for the clinical details of the study participant to reduce the bias. UKPDS brain bank criteria was used to diagnose idiopathic PD, NINDS-SPSP for Progressive supranuclear palsy and European consensus criteria for Multiple system atrophy. Clinical assessment of PD patients was done using modified Hoehn and Yahr staging.

Statistical Analysis

Data was entered in excel-2007, analysis of data was done using SPSS-16 version. Descriptive data was presented as frequencies and percentages. Unpaired t-test was applied to find the statistical difference between means. Data representation was done by appropriate pie charts, bar diagram and box plots for median. Data was tabulated as per the content appropriate.

Ethical Considerations

Written informed consent was obtained from the patients. Confidentiality of the patients was maintained by blinding the case report forms and not mentioning their personal details.

RESULTS

The study included 50 patients fulfilling the inclusion criteria with symptoms of parkinsonism. Detailed clinical history was noted about the onset, progression of the symptoms, categorized under typical or atypical parkinsonism groups after neurological examination. All patients were subjected to 3 T MRI Brain and DTI study was taken up as a substudy in neuroimaging which was done in 25 patients and 10 controls.

Baseline characteristics of cases and controls were matched for age and gender.

Gender Distribution

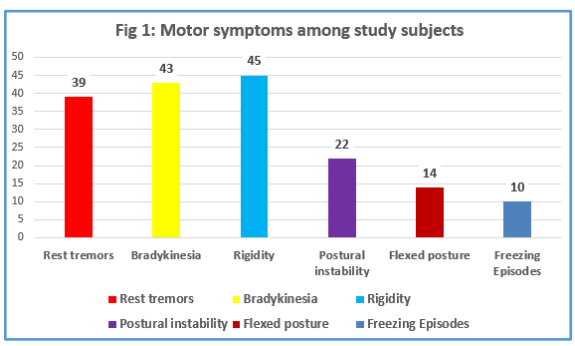
Of the 50 cases 34 (68%) were males and 16 (32%) were females.

Age

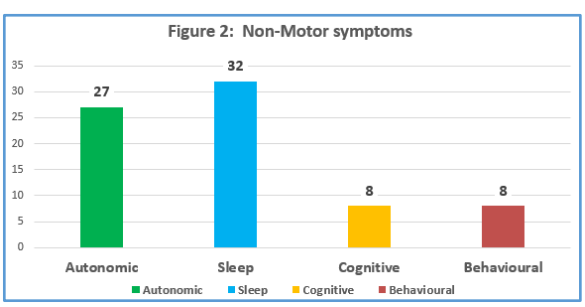
The age range for cases was 24 yrs. to 70 yrs. Most of the cases were in the age group of 40-60 yrs. Mean age of presentation for cases was 49.94 yrs. Male population represented higher cases than females in all age groups of the study.

Co- Morbidities

Hypertension, diabetes and coronary artery disease (CAD) were the most common comorbidities documented. Hypertension was documented in 16(32%) of the patients, followed by CAD in12 (24%) and diabetes in 10 (20%).Combination of all 3 risk factors was noted in 3 (6%) patients. No risk factors were present in 25 (50%) patients.



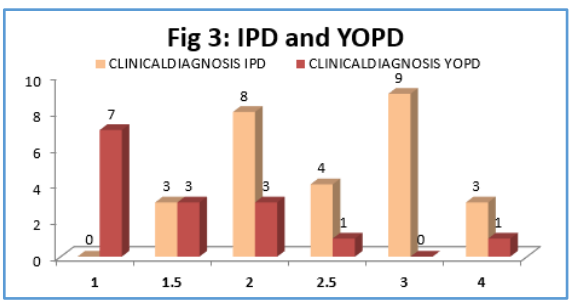
Motor Symptoms



Non – Motor Symptoms

Clinical Diagnosis

Typical parkinsonism group included idiopathic PD - 27 (54%) patients and young onset PD – 15 (30%) patients, total constituting about 42 (84%) patients. 8 (16%) patients had atypical features categorized under PSP- 6(12%) patients and MSA – 2(4%) patients.



UPDRS Results

Mean score of total UPDRS including parts I, II, III in in the study was 66.78. Median UPDRS- III motor scale for atypical PD patients was 55 and typical PD patients was 36.

MRI Profile

Among the 50 patients 9 (18%) patients had diffuse cerebral atrophy, 9(18%) patients had small vessel disease with lacunar infarcts on MRI brain imaging. Midbrain atrophy with 'humming bird' sign was found in 4(8%) patients of progressive supranuclear palsy. Other 2 patients with clinical diagnosis of PSP showed normal MRI.

In 2 patients with clinical diagnosis of MSA, one patient MRI showed 'Hot cross bun' sign and other showed olivopontocerebellar atrophy. Normal MRI was documented in 26(52%) patients.

DTI Imaging

Among the 25 patients and 10 controls in whom DTI was performed, fractional anisotropy values were obtained from cingulate cortex, basal ganglia, corticospinal tracts, superior longitudinal fasciculus, substantia nigra, thalamus regions of brain. Additionally, in MSA patients, middle cerebellar peduncle and pons regions were also obtained and compared with controls.

Mean FA Values	PD	Controls	P-value
FACI	0.65095	0.68945	0.064
FAGP	0.31698	0.2885	0.194
FAIC	0.71475	0.72145	0.111
FACST	0.73483	0.76085	0.104
FAPU	0.18994	0.17905	0.315
FASLF	0.62409	0.62025	0.801
FASN	0.4256	0.44801	0.076
FATH	0.25525	0.25205	0.741

Table 1. DTI Analysis- Mean Fa Values Comparison

FA-Fractional anisotropy, CI –cingulate cortex, GP – globus pallidus, IC –internal capsule, CST- corticospinal tract, PU –putamen, SLF – superior longitudinal fasciculus, SN –substantia nigra, TH - thalamus

Among all regions of brain studied, mean FACI and FASN values were significantly lower in PD patients when compared to controls. (FACI p-value = 0.064, FASN p-value = 0.076)

None of the mean FA values showed statistically significant difference between patients and controls.

We also looked for any difference in mean FASN values in late onset PD group when compared with controls. Results are shown in table 14.

	FASN Values	p-value
Cases	0.4268	
Controls	0.4504	0.178 (NS)

Table 2. Comparison of FASN Values for Late Onset PD vs Controls

The mean FASN values of late onset PD patients when compared to controls, was lower but statistically not significant (p-value = 0.178)

Comparison of mean FA values in middle cerebellar peduncle and pons regions in MSA patients and controls is shown in table 15.

	MSA	Control	p-value
FAMCP	0.660	0.7467	0.188 (NS)
FAPN	0.5102	0.6975	0.0675 (NS)

Table 3. Comparison of Specific FA Values in MSA Patients vs Controls

The mean FA values of middle cerebellar peduncle and pons regions in MSA patients when compared to controls, was lower but statistically not significant. (p value = 0.188 and 0.067 respectively).

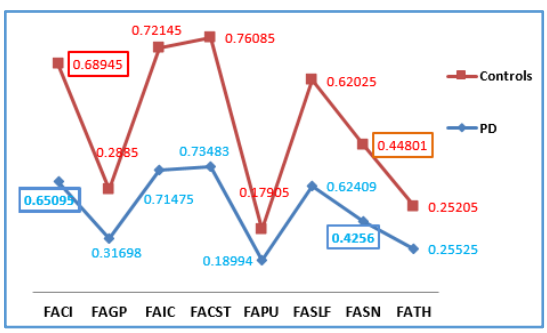


Figure 4. FA Values among Cases and Controls

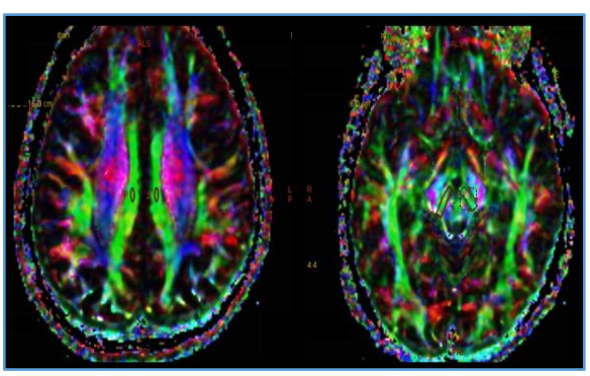


Figure 5. Colour Coded Orientation Maps

Cingulate cortex region Substantia nigra region

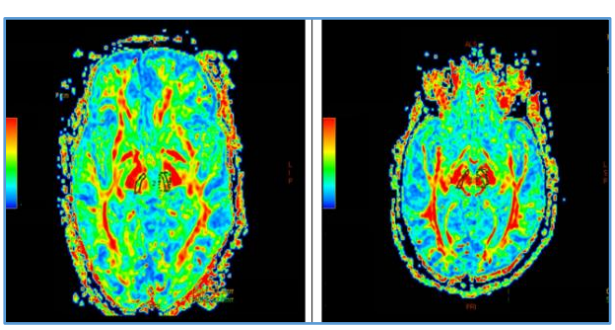


Figure 6. Region of Interest – Substantia Nigra

Fractional anisotropy values comparison
Patient (Av - 0.366,0.401) Control (Av – 0.520,0.475)

DISCUSSION

68% of the patients were males and the rest were females in the study. The male female ratio is 2.1 suggesting the male gender risk of developing Parkinson's Disease is more. The majority of studies support an excess of male to female cases. The average ratio of male to female standardized rates is 1.35 from prevalence studies and 1.31 from incidence studies, but the range of values is wide.[5]

The clinical presentation of patients in the present study pertaining to motor symptoms are compared with Hoehn and Yahr study.[6]

	Symptoms	Present study No. (%)	Hoehn.M,[6] Yahr M
Motor	Rest tremor	39 (78)	70%
	Bradykinesia	43 (86)	90%
	Rigidity	45 (90)	90%
	Postural instability	22 (44)	21%
	Flexed posture	14 (28)	18%
	Freezing episodes	10 (20)	18%

Table 4. Motor Symptoms

The proportion of PD patients with rest tremor has been reported to be 90% in clinical series by Hoehn MM, Yahr MD[6] and 76–100% in postmortem series study done by Rajput AH et al.[7]

Prevalence of other motor symptoms i.e bradykinesia, rigidity, postural instability, flexed posture, freezing episodes was similar to the reported literature.

Non- Motor Symptoms

The importance of nonmotor symptoms in the diagnosis is also crucial in PD. Autonomic dysfunction was seen in 54% of the patients in the study, while study done by Zesiewicz TA et al.,[8] reported 70-80% of autonomic dysfunction in their study.

Raghothaman *et al.*,[9] studied patients of PD and PD from MSA (MSA-P) to find if the presence of dysautonomic symptoms such as urinary incontinence and orthostatic symptoms, would help in the diagnosis of these disorders. It was found that when these symptoms are present within one year of illness, they can accurately point towards the diagnosis of MSA-P. Our study also noticed dysautonomic manifestations from both history and examination in both MSA pts within one year of symptoms and helped in early diagnosis and management.

Sleep disturbances were seen among 64% of the patients in the present study which was lesser than a community-based study done by Factor SA and McAlarney T et al.[10] Insomnia was present in 36% pts, excessive daytime sleepiness in 18% pts and RBD in 10% pts, none reported restless leg syndrome.

Cognitive dysfunction was observed among 16% of the patients in the present study. Pfeiffer HC, et al reported in their study 69% of patients showed episodic memory deficits, 54% executive dysfunction, 50% language/praxis deficits, 46% visuospatial/constructional deficits and 35% attention/working memory deficits.

Behavioural disturbances was found to be 16% in the present study while reviews of prior work indicate that about 40% of PD patients suffered from one or the other behavioural disturbances. Major depression was the commonest disturbance reported in 8% pts. Scott B et al,[11] examined a sample of 948 patients and found that 36% of PD patients complained of depression. However, depression was not identified by the patients as the most distressing symptom. A population-based study of 97 PD patients found that 36.1 % reported mild depressive symptoms, while another 10% reported moderate and severe symptoms.[12] In a small community-based New Zealand study, the prevalence of major depression was 2.7% and overall prevalence of mood and anxiety disorders was 6.8% in non -demented PD patients.[13]

In neuroimaging, biomarkers are measures derived from images that reflect the presence of diseases or their severity and that can be used for early diagnosis, prognosis or to monitor responses to therapeutic interventions. Biomarkers are expected to detect early neuropathological features and mechanisms underlying neurodegeneration in PD and to correlate with disease progression in order to allow the monitoring of disease status. Ideally, they should be able to detect preclinical changes. Reliable biomarkers need to be confirmed by independent studies.

As many studies on DTI in parkinsonism focused on group analyses and evaluating patients in advanced disease stages, the challenge now lies in clinical application of quantitative DTI in the diagnostic workup of an individual patient presenting with parkinsonism. Our study mainly used ROI method for studying both gray and white matter in brain of PD patients.

In the present study none of the mean FA values in DTI imaging showed statistically significant difference between the patients and controls. Specifically, the mean FA value of the substantia nigra (0.4256 vs 0.44801, p=0.076) which was supposed to be crucial finding in patients with PD and FA value of cingulate cortex region was lower compared with controls but found to be not statistically significant. The present findings were similar to the study done by Chan et al[14] where 73 PD patients and 78 controls were taken up for ROI analysis in caudate, globus pallidus, putamen, substantia nigra and thalamus and found out statistical significance only in substantia nigra region (Mean FA values, 0.403 vs 0.415, p=0.001). Rest of the regions studied didn't show any variation when compared to controls.

Additionally, in our study we also found cingulate cortex region (Mean FA values, 0.65095 vs 0.68945, p=0.064) affected apart from substantia nigra region. Matsui et al[15] studied 26 PD patients, subdividing into two groups -PD with dementia group and PD without dementia group using ROI analysis in frontal, temporal, occipital, parietal, cingulate bundles. The PD dementia group showed significant FA reduction in the bilateral posterior cingulate bundles compared with PD without dementia group.

Our results support post-mortem findings that the substantia nigra is the most severely affected primary site of pathology in this condition.[16] 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 less number of the most severe PD cases from the study. Interestingly, the FA values in the substantia nigra were higher than those of the thalamus, which was also the finding of Yoshikawa and colleagues, where in detailed tracing and drawing of multiple ROIs along a postulated nigrostriatal pathway was employed.[17]

Although there appears to be a linear trend of FA decreasing across PD subgroups, there was no statistically significant difference among PD subgroups. But in the present study we could not separately study for the rostral and caudal segments in SN but overall showed a decreased trend in FA values in patients when compared to controls.

In the present study, the mean FA values of MSA patients in middle cerebellar peduncle and pons region when compared to controls, was lower but statistically not significant. (p values 0.188 and 0.067 respectively).

These ROI's i.e middle cerebellar peduncle and pons region in PD patients is lower when compared to the controls suggesting the atrophy of these regions. In a study done by Mizuki Ito.et.al,[18] where both ROI and tract-based analysis was done in 21 PD patients and 20 controls, results showed MSA patients had low FA values when compared with controls. In another similar type of study done by Blain et.al,[19] where ROI approach was used to measure changes in FA values in the middle cerebellar peduncles, decussation of the superior cerebellar peduncles, and pons in 17 patients with MSA vs 12 controls, FA values were markedly reduced in the middle cerebellar peduncles and in pons compared with controls in MSA patients.

However, in both studies, Mizuki Ito et.al, and Blain et.al, FA values did not show statistical significance but showed only lower FA values.

	No. of Cases	No. of Controls	Direction No.	Region Studied	FA values
Present study	25	10	25	CI,IC,GP,PU, CST,SLN,TH,SN MCP	CI↓ SN ↓
Yoshikawa et al	12	8	6	PMC, SN,BG	SN ↓
Chan et al	73	78	12	GP,PU,SN,TH	SN↓
Menke et al	10	10	60	SN	No variation
Focke et al	12	13	24	GP,SN,PU,CA	No variation

Table 5. Comparison of DTI Studies

Our study DTI findings using ROI analysis helped in differentiating typical vs atypical PD syndromes and also diagnosing PD patients at an early stage who had normal standard MRI brain imaging.

CONCLUSION

1. Male population represented higher cases than females. Mean age of presentation for cases was 49.94 yrs and mean duration of the symptomatology was 2.25 years. Asymmetrical onset of symptoms was seen in 72% patients.
2. Among the motor symptoms- rigidity, bradykinesia and rest tremor were present in more than 75% pts whereas postural instability, freezing episodes were present in around 15% patients. Among the non-motor symptoms – autonomic and sleep disturbances were the common presentation in around 30% pts whereas cognitive and behavioural symptoms were present in 8% patients.
3. In the present study typical PD patients constituted 84% and atypical PD 16%. Among the typical PD 54% patients came under IPD and 30% patients were YOPD. In the atypical PD group 12% patients were PSP and 4% patients were MSA.
4. Median UPDRS- III motor scale for atypical PD patients was 55 and typical PD patients was 36. These results show that the burden of morbidity in atypical PD patients was more when compared with the typical PD pts and also depends on the stage of the disease.
5. The mean FASN values of late onset PD patients when compared to controls, was lower but statistically not significant. None of the FA values showed statistically significant difference between patients and controls but showed a decreased trend in comparison with the previous studies.
6. The mean FA values of MSA patients in Middle cerebellar peduncle and pons region when compared to controls, was lower but statistically not significant. Even though there was no statistical significance among core parameters obtained, this study reinforces the findings in terms of trends in FA values thereby establishing the role of DTI in detecting the early changes in PD syndromes.
7. Our study DTI findings using ROI analysis helped in differentiating typical vs atypical PD syndromes and also diagnosing PD patients at an early stage who had normal standard MRI brain imaging.

REFERENCES

[1] Jankovic J. Parkinson’s disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79(4):368-376.

[2] Behari M, Bhattacharyya KB, Borgohain R, et al. Parkinson's disease. Annals of Indian Academy of Neurology 2011;14(5):2-6.

[3] Zhang L, Liu J. The role of neuroimaging in the diagnosis of Parkinson’s disease. International Journal of Integrative Medicine 2013;1:1-5.

[4] Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003;4(6):469-480.

[5] Zhang ZX, Roman GC. Worldwide occurence of Parkinson's disease: an updated review. Neuroepidemiology 1993;12(4):195-208.

[6] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(5):427-442.

[7] Rajput AH, Rozdilsky B, Ang L. Occurrence of resting tremor in Parkinson’s disease. Neurology 1991;41(8):1298-1299.

[8] Zesiewicz TA, Baker MJ, Wahba M. Autonomic nervous system dysfunction in Parkinson's disease. Curr Treat Options Neurol 2003;5(2):149-160.

[9] Ragothaman M, Swaminath PV, Sarangmath N, et al. Role of dysautonomic symptoms in distinguishing Parkinson’s disease (PD) from multiple system atrophy (MSA-P) within a year of developing motor symptoms. J Assoc Physicians India 2011;59:95-98.

[10] Factor SA, McAlarney T, Sanchez-Ramos JR, et al. Sleep disorders and sleep effect in Parkinson’s disease. Mov Disord 1990;5(4):280-285.

[11] Scott B, Borgman A, Engler H, et al. Gender differences in Parkinson's disease symptom profile. Acta Neurol Scand 2000;102(1):37-43.

[12] Schrag A, Jahanshahi M, Quinn NP. What contributes to depression in Parkinson's disease? Psychol Med 2001;31(1):65-73.

[13] Hantz P, Caradoc-Davies G, Caradoc-Davies T, et al. Depression in Parkinson's disease. Am J Psychiatry 1994;151(7):1010-1014.

[14] 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(12):1383-1386.

[15] Matsui H, Nishinaka K, Oda M, et al. Dementia in Parkinson’s disease: diffusion tensor imaging. Acta Neurol Scand 2007;116(3):177-181.

[16] Abe O, Aoki S, Hayashi N, et al. Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. Neurobiol Aging 2002;23(3):433-441.

[17] Yoshikawa K, Nakata Y, Yamada K, et al. Early pathological changes in the parkinsonian brain demonstrated by diffusion tensor MRI. J Neurol Neurosurg Psychiatry 2004;75(3):481-484.

[18] Ito M, Watanabe H, Kawai Y, et al. Usefulness of combinedfractional anisotropy and apparent diffusion coefficientvalues for detection of involvement in multiplesystem atrophy. J Neurol Neurosurg Psychiatry 2007;78(7):722-728.

[19] Blain CR, Barker GJ, Jarosz JM, et al. Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. Neurology 2006;67(12):2199-2205.