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Original Article

Efficacy of I-131 MIBG Myocardial Scintigraphy for the Differentiation Between Parkinson's Disease and Multiple System Atrophy

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ABSTRACT

Objective: To assess efficacy of I-131 Metaiodobenzylguanidine Myocardial Scintigraphy for differentiation between Parkinson's Disease and Multiple System Atrophy.

Study Design: Validation Study.

Place and Duration of Study: Department of Neurology, Pakistan Emirates Military Hospital, Rawalpindi Pakistan, from May 2019 to Jan 2022.

Methodology: Undiagnosed patients with motor and autonomic symptoms of Parkinsonism were enrolled. I-131 Meta-iodobenzylguanidine Myocardial Scintigraphy was performed and subjects were diagnosed as per early (15 min) and late (4h) heart/mediastinum ratios with washout ratio. At the same time, patients were reviewed for clinical diagnosis using clinical criteria, radiological studies and followed up for 2 years or till definitive clinical diagnosis was formed. Sensitivity and Specificity of I-131 Metaiodobenzylguanidine for Diagnosis of Parkinson's Disease and Multiple System Atrophy was calculated.

Results: Out of 79 patients, 48 were diagnosed with Parkinson's Disease, 15 with Multiple System Atrophy and 16 fell in criteria for other diseases. Early heart/mediastinum, Late heart/mediastinum and washout ratio in Parkinson's group was 1.53±0.19, 1.39±0.18 and 37.20±17.91, in Multiple System Atrophy was 2.02±0.10, 2.00±0.11 and 11.35±9.46 and in others was 2.36±0.18, 2.41±0.18 and 0.40±22.49 respectively. This revealed a sensitivity and specificity of 83.67% and 76.67% for Parkinson's Disease and 66.67% and 92.19% for Multiple System Atrophy respectively.

Conclusion: I-131 Metaiodobenzylguanidine can be used to help in differential diagnosis of Parkinsonism with autonomic features, with good sensitivity and specificity.

Keywords: 3-Iodobenzylguanidine, Metaiodobenzylguanidine, Multiple System Atrophy, Parkinson Disease, Sympathetic Nervous System.

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INTRODUCTION

Parkinson's Disease (PD) and Multiple System Atrophy (MSA) are neurodegenerative synucleinopathies characterized by deposition of alpha-synuclein throughout central and peripheral nervous system.[1] Although management strategies of both illnesses differ considerably, they might have similar clinical onset and it can be especially challenging to differentiate Multiple System Atrophy from PD.[2,3] Magnetic Resonance Imaging (MRI) of brain is widely used to differentiate between the two.[4,5] Abnormal MRI findings in MSA may be absent in early disease which could delay diagnosis. In PD, MRI typically remains normal.[5] This, in conjunction with low specificity of MRI in general to distinguish MSA from other Parkinsonian syndromes further prompts exploring alternative imaging modalities.[6]

Autonomic dysfunction is a common feature of MSA and PD. In PD, degeneration of both preganglionic and postganglionic fibers is observed whereas in MSA predominantly preganglionic degeneration occurs.[7] Thus, postganglionic sympathetic degeneration can be used to differentiate PD from not only MSA but also from other causes of Parkinsonism.[8]

Postganglionic denervation can be detected using I-123 Metaiodobenzylguanidine (MIBG) or I-131 MIBG scintigraphy.[9] MIBG possesses a structural similarity to norepinephrine and is recognized and actively taken up and stored in postganglionic sympathetic nerve terminals. MIBG is stored in norepinephrine vesicles in postganglionic sympathetic nerve terminals while non-neuronal (type 2) uptake is quickly wiped out.[10] This reuptake helps in visualizing cardiac

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sympathetic innervation and as such can help differentiate among these conditions.

This study firstly aims to establish validity of I-131 MIBG, as it has been uncommonly used as compared to I-123 MIBG for diagnosis of PD and MSA, and secondly, to validate this method prospectively as most of previous studies done on this subject have been retrospective. Thirdly, to study this method in South Asian population, where this method has not been studied earlier.

METHODOLOGY

This prospective observational study was conducted at Department of Neurology, Pak Emirates Military Hospital and Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from May 2019 to Jan 2022 after approval from the Institutional Ethical Review Board (letter no Cons-NMC-1/READ-IRB/879).

Inclusion Criteria: Undiagnosed patients of either gender, belonging to any age group, reporting to Department of Neurology with features of Parkinsonism with dysautonomia were included.

Exclusion Criteria: Patients previously diagnosed with Parkinsonism with dysautonomia with either PD or MSA, diseases interfering with MIBG reuptake such as Ischemic heart disease or cardiac failure, medications that interfere in MIBG uptake at nerve terminal that include combined alpha/beta blockers (Labetalol, Carvedilol), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors SNRIs, Amphetamines or Cocaine, patients with previous history of CNS disease such as encephalitis, stroke or head injury, patients with thyroid disease, allergy to iodine & long-term diabetes with neuropathy were excluded.

As this is a rare modality to diagnose these conditions, we took as many patients as available over the course of study, which was 112. Twenty-seven of these were lost to follow-up over the two-year study period, and six patients received their diagnosis based on clinical findings, hence were excluded, which brought our total sample size to 79. Non-probability consecutive sampling was employed to recruit patients.

Parkinsonism was defined as patients with Bradykinesia (slowness of movement with decrement in amplitude/speed or progressive halts as movements are continued), Rigidity (resistance to passive movement of major joints while in a relaxed position) and Rest Tremors (4-6 Hz tremor observed in fully resting limb. Autonomic dysfunction was defined by anyone of symptoms such as orthostatic hypotension, urinary symptoms (retention or incontinence) or positive Tilt test.

Detailed history was taken including age of patients, gender, duration of symptoms, severity of symptoms and family history. Detailed general physical examination including postural drop and detailed neurological examination was performed. Patients with unclear autonomic signs were tested with Tilt Test. All included patients underwent MRI Brain.

All selected patients underwent I-131 MIBG myocardial scintigraphy following thyroid blockage with oral 1% Lugol's solution at a dose of 1 drop/kg to max 40 drops per day divided in 2 doses starting a day before and continuing for 5 days after scan. Patients were administered 1.2 millicurie (mCI) of intravenous I-131 MIBG followed by 15 min and 4h \nterior planar images of chest using dual headed gamma camera (Siemens Evo Excel) using High energy collimator. A 20% window centered at 364 keV was set for 131I photopeak. Images were processed by two experienced nuclear physicians by drawing Regions of Interest (ROI) over heart and mediastinum. Heart and mediastinum uptake ratios (H/M) were calculated by average counts per pixel in heart and mediastinum at 15 mins (H/M early) and 4 hours (H/M late). Washout ratio (WOR) was calculated by formula: WOR=[{H(early)-M(early)}-{(H(late)-M(late)}] / [H(early)-M(early)]. H/M (early and late) and WOR among PD, MSA and other conditions were taken as per findings of Yang *et al*. and given as in Table-I.[9]

Table-I: Reference Range for Heart and Mediastinum Uptake and Washout Ratio for each Disorder

Group	H/M Ratio		Washout Ratio (%)
	Early	Late	
Parkinson's Disease	≤1.84	≤1.77	>15%
Multiple System Atrophy	>1.8-≤2.26	>1.7-≤2.19	≤25
Others	>2.15	>2.19	≤5

Following testing, all patients were followed-up for 2 years or till a clinical diagnosis was made either by clinical criteria (MDS diagnostic criteria for PD and second consensus statement for MSA) or with aid of imaging studies by neurology team.[11,12] I-131 MIBG myocardial scintigraphy results were then compared

with clinical diagnosis to find out sensitivity and specificity of diagnostic study.

Data was recorded, compiled and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Continuous variables such as age were expressed as Mean±SD. Categorical variables were expressed as frequencies and percentages.

RESULTS

A total of 112 individuals were enrolled in this study after detailed history and application of inclusion and exclusion criteria. Twenty-seven patients were lost to follow up and in 6 patients' definitive diagnosis was made through clinical means in the study period, hence they were excluded from the study. This resulted in final tally of 79 individuals, of which 56(70.9%) were males and 23(29.1%) were females. Mean age of study group was 61.29±11.96 years. Most individuals in the study had early disease with a mean duration of illness of 2.56±1.57 years. Common motor and autonomic symptoms seen in this group are summarized in Table-II. Other motor symptoms include speech and swallowing issues, REM sleep disorder or restless legs syndromes.

Table-II: Frequency of Motor and Autonomic Symptoms in Study Population (n=79)

Group	Symptom	Frequency n(%)
Motor Symptoms	Resting Tremor	61(77.22)
	Bradykinesia	63(79.75)
	Rigidity	53(67.09)
	Postural instability	41(51.9)
	Other	28(35.44)
Autonomic Symptoms	Postural Hypotension	44(55.70)
	Urinary incontinence	28(35.44)
	Urinary Retention	16(20.25)
	Positive Tilt Test	21(26.25)

Using our diagnostic test and after application of reference ranges, 48 individuals were diagnosed with PD from our study group, 15 individuals with MSA and 16 as other illnesses. Average Early H/M, Late H/M and WOR for each group are given as in Table-III.

Table-III: Average Early H/M, Late H/M and Washout Ratios in Patients (n=79)

Group	H/M Ratio		Washout Ratio
	Early	Late	
Parkinson's Disease	1.53±0.19	1.39±0.18	37.20±17.91
Multiple System Atrophy	2.02±0.10	2.00±0.11	11.35±9.46
Others	2.36±0.18	2.41±0.18	0.40±22.49

**H/M: Heart and Mediastinum*

H/M and Late H/M of individuals diagnosed with PD were found to deteriorate when compared with duration of symptoms, while in case of MSA these appear to stay constant.

After 2 years of regular follow-up and use of clinical criteria and imaging studies, all study subjects were given a definitive clinical diagnosis. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value for diagnosis of PD and MSA was calculated and are given in Table-IV.

Table-IV: Diagnostic Characteristics of I-131 MIBG in Diagnosis of PD and MSA

Group	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Parkinson's Disease	83.67	76.67	85.42	74.19
Multiple System Atrophy	66.67	92.19	66.67	92.31

**MIBG: Metaiodobenzylguanidine, PD: Parkinson's Disease, MSA: Multiple System Atrophy*

Out of 48(60.7%) individuals diagnosed with PD through combination of neurological follow-up and radiological studies, 41(85.42%) were correctly diagnosed through I-131 MIBG scan. This yielded a diagnostic accuracy of 81.01%. Seven (14.58%) individuals were incorrectly labelled with PD, out of which 3(6.25%) were later diagnosed with MSA, 2(4.17%) with Essential Tremor and 1(2.08%) each with Corticobasal Degeneration and Lewy Body Dementia. Four out of the 15(26.67%) individuals diagnosed with MSA through our diagnostic test were later found to have PD, while 4 out of 16(25%) individuals screened out were later diagnosed with PD. Of note these 8 individuals had relatively early disease with mean duration of illness 1.685±0.70 years.

A total of 15(18.99%) individuals were diagnosed with MSA through clinical follow up and radiological studies, however out of these, only 10(66.67%) were diagnosed correctly by I-131 MIBG scan. Four out of 15(26.67%) individuals with PD and 1 out of 15(6.67%) with Essential Tremor were incorrectly labelled with MSA, while 4 out of 48(8.33%) patients labelled with PD and 1 out of 16(6.25%) screened out patients were later clinically diagnosed with MSA. This yielded a diagnostic accuracy of 88.61%.

Out of the remaining 16 patients, after follow-up, 6(37.5%) were diagnosed with Essential Tremor, 3(18.75%) with Progressive Supranuclear palsy, 3(18.75%) with Corticobasal Degeneration, 2(12.5%)

with Lewy Body Dementia and 2(12.5%) with functional symptoms.

DISCUSSION

Cardiac I-131 MIBG scan is a relatively newer technique to diagnose cause of Parkinsonism in cases where clinical diagnosis is difficult due to overlapping features in early diseases. It is a non-invasive test and is being used to guide treatment in such cases.

Using diagnostic criterion mentioned above, we observed a sensitivity and specificity of 83.67% and 76.67% in diagnosis of PD and 66.67% and 92.19% in diagnosis of MSA respectively. A comparison of sensitivity and specificity of this method with previous studies in summarized in Table-V.

Another aspect highlighted in our study was progressive decline in early and late H/M ratio in case of PD but not in MSA. This indicates progressive decline in sympathetic innervation and progressive autonomic degradation with disease progression. This might indicate that in very early PD, this test might not be as sensitive however further studies might be required to ascertain this. This is further supported in our study by subgroup of PD patients who tested for MSA or screened out had relatively earlier disease when compared with rest of patients.

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Table-V: Comparison of Study Results with Previous Documented Studies

Disease	Study	Isotope Used	Study Method	Number of Subjects	Sensitivity (%)	Specificity (%)
Diagnosis of Parkinson's Disease	Our Study	I-131	Prospective	79	83.67	76.67
	Xu et al.[13]	I-131	Retrospective	44	95	94
	Braune et al.[14]	I-123	Retrospective	20	100	100
	Chen et al.[15]	I-131	Retrospective	54	Up to 91.7	Up to 92.6
	Kawazoe et al.[16]	I-123	Prospective	600	Up to 86.3	Up to 91.7
	Ryu et al.[17]	I-123	Retrospective	188	Up to 89.5	Up to 96.2
Differentiation between PD & MSA	Our Study	I-131	Prospective	79	66.67	92.19
	Fujita et al.[18]	I-123	Retrospective	139	70.3	86.8
	King et al.[19]	I-123	Meta Analysis of retrospective studies	2680	94	91
	Treglia et al.[20]	I-123	Meta Analysis of retrospective studies	1226	89	77

**MSA: Multiple System Atrophy, PD: Parkinson's Disease*

Compared to previous studies, sensitivity and specificity seems to be on the lower side but this can be explained when considering prospective nature of this study which resulted in selection of sample population with undiagnosed and early disease. Compared to only prospective study in this group our results show a sensitivity and specificity of 83.67% and 76.67% vs 86.3% and 91.7% shown by Kawazoe *et al*.[16] Still, the results of this study are promising and concur with previous belief that cardiac sympathetic fiber involvement precedes neuronal cell loss in PD.[21] Hence an early diagnosis can be made using this method even in premotor stage of PD.

We used a cutoff value of 1.77 for Late H/M on basis of one study.[18] which as one of the pioneering studies for utilization of I-131 MIBG for this purpose. Similarly, a meta-analysis done by King *et al*. also recommended a cutoff of 1.77 for late H/M for 1-123 for best results.[19] Furthermore, we recommend combination of all Early H/M, Late H/M and WOR to diagnose each disorder.

LIMITATION OF STUDY

Few limitations of study include exclusion of major subset of population with heart disease, thyroid disease, diabetes with neuropathy and individuals on certain common medications. This forms a significant subset of population in the age group where this test might be required, however as theoretically these conditions and medications interfere with uptake of MIBG they might interfere with study results. Further studies may be done to compare H/M and WOR in individuals with and without mentioned confounding factors to throw further light at the subject.

CONCLUSION

This study further builds on previous evidence on utility of I-131 MIBG in differential diagnosis of Parkinsonism at an early stage using above mentioned cutoff values. It proves its effectiveness in true clinical cases in a prospective fashion and its utilization in South Asian population.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MH & FH: Conception, study design, drafting the manuscript, approval of the final version to be published.

AM & MNAK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

ZS & MR: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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