The potential role of the cardiac MIBG scan in differentiating the
drug-induced Parkinsonism from Parkinson’s disease

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Abstract

Introduction: Considering the difficulties of differentiating Parkinson’s disease (PD) from drug-induced Parkinsonism (DIP) in patients receiving antipsychotics, developing robust diagnostic tools is essential. Herein, we used the metaiodobenzylguanidine (MIBG) scan to assess its diagnostic accuracy for this purpose.

Methods: 44 DIP patients and 32 patients with PD as controls were enrolled. All the participants underwent a cardiac 123I-MIBG scan. Statistical analysis was conducted to determine the significance of the results, and accuracy analyses were conducted to calculate the related sensitivity and specificity of the MIBG scan.

Results: The mean age of PD and DIP groups were 62.6 ± 5.9 and 51.5 ± 10.8 years, respectively. The mean duration of drug consumption in the DIP group was 52.2 ± 29.4 days (the mean interval between drug initiation and DIP onset was 28.5 ± 20.5). Symptoms relief occurred 40 ± 24.2 days after drug discontinuation. In the PD group, 15.6% showed negative and 84.4% positive results on the MIBG scan. In the DIP group, 86.4% were negative, and the remaining were positive. The difference in MIBG uptake between the two groups was statistically significant (P-value < 0.001). The sensitivity and specificity of the MIBG scan were 84.4% (CI: 84.0–84.8) and 86.36% (CI: 86.0–86.7) for the diagnosis of PD, respectively.

Conclusion: Our results indicated more positive MIBG scans in the PD group than the DIP. Also, the MIBG scan’s sensitivity and specificity in differentiating the PD are acceptable. Future works should assess these findings and the role of the MIBG scan in prognosis assessment of DIP and better allocation of the patients to related disciplines.

Keywords:
Parkinson’s disease
Drug-induced Parkinsonism
123I-metaiodobenzylguanidine (MIBG)

1. Introduction

Parkinson’s disease (PD), as the second most prevalent neurodegenerative disease with an increasing rate of occurrence, comprises remarkable referees to the neurologic and psychiatric clinics worldwide [1]. The well-known manifestation of PD, including resting tremor in one hand (often accompanied by decreased arm swing during walking), muscle stiffness, rigidity, and slowness of movement (Bradykinesia), facilitates the diagnosis [2,3]. Nevertheless, relatively lower consideration is given to differentiate other types of Parkinsonism, particularly drug-induced Parkinsonism (DIP), which is mainly related to using the first generation of antipsychotic drugs with an occurrence of 20 to 35% of patients [4].

To consider a PD diagnosis, detecting two out of four symptoms, including bradykinesia, tremor, rigidity, and postural reflex disorders is essential. A DIP diagnosis is considered when the onset of the symptoms is within six months of starting dopamine-lowering or blocking medications. The patient has no prior history of movement disorders, and the symptoms cease entirely within six months of stopping the suspected medication [5]. Also, a gender difference is noted in this regard, and DIP is indicated to be about 10% more common in females [5].

The diagnostic challenges to discriminate DIP from PD necessitated...
developing diagnostic aids to accelerate and facilitate the diagnosis. This is particularly important due to a difference in the required therapeutic and patent referral approaches. In this regard, studies have suggested using nuclear scans (i.e., scans assessing dopamine receptor function, dopamine transporter activity, and epinephrine reuptake capacity) that can potentially differentiate neurodegenerative PD from other symptomatic Parkinsonisms [6,7]. Combining clinical diagnosis with these scans is suggested to alter the diagnosis in up to 40% of suspected patients, remarkably affecting the required therapeutic interventions [8]. Also, considering the increasing availability, ever-improving performance, and reasonable cost of the metaiodobenzylguanidine (MIBG) cardiac scintigraphy, this modality is a remarkable potential candidate as a paraclinical aid in DIP diagnosis [9]. Former works suggest that the heart to mediastinum (H/M) ratio on 123I-MIBG scans is significantly higher in atypical Parkinsonism than in the primary PD. Furthermore, DIP patients with a low H/M Ratio had a poorer prognosis [10]. Previously, we employed 131I MIBG, which is available more widely and less costly, instead of 123I MIBG to differentiate Lewy body dementia (LBD) from Alzheimer disease(AD) with promising results [11].

Accordingly, due to the diagnostic challenges of differentiating DIP from PD and the current promising literature on the utility of cardiac (123I)-MIBG scintigraphy in diagnosing neurodegeneration, we aimed to investigate the potential diagnostic utility of a similar less expensive and more acceptable radioactive trace, (131I)-MIBG scan, as a robust diagnostic tool to ease and accelerate the diagnosis.

2. Methods

2.1. Design and participants

In this cross-sectional study, we prospectively enrolled 44 patients with drug-induced Parkinsonism (DIP) and 32 patients with Parkinson’s disease (PD) referred to our psychiatry and neurology clinics affiliated with the Tehran University of Medical Sciences for the diagnostic evaluation and treatment. All DIP patients were diagnosed using the following three criteria: (1) presence of at least two of the four cardinal signs (tremor, rigidity, bradykinesia, and impaired postural reflexes), (2) absence of a history of extrapyramidal disorders before treatment with the antipsychotics and (3) onset of symptoms during the course of treatment with the antipsychotic drug. Among patients who experienced DIP symptoms, none had a prior history of Parkinsonism, but all had a prior psychiatric diagnosis of psychosis or mood disorder. During the study period, DIP patients were not taking any anti-parkinsonism drug. The selected criteria were determined based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition DSM-V [12].

All patients with PD were diagnosed according to the UK Parkinson’s Disease Society Brain Bank (UKPDSBB) clinical diagnosis criteria [13]. The clinical stages of Parkinsonism were assessed according to the classification of Hoehn and Yahr. All patients with a history of other neuropsychological diseases, family history of other neuropsychological diseases, and previous or current cardiac disease were excluded from this study. None of these patients were cigarette smokers, alcohol drinkers, or stimulant drug users. Routine chest radiography and electrocardiography revealed no abnormalities. Lastly, patients were categorized with regards to receiving either typical or atypical antipsychotics based on the latest available reference [14].

2.2. Definitions

For the cardiac uptake experiments, 1.4–2 mCi 131I-MIBG was injected intravenously, and imaging was done 2 h later, using a dual-head gamma camera system (Any scan, Mediso Co.,). Standard radiation protection protocols were employed. Static images were acquired for 8 min using a high-energy collimator at peak 131I photopeak with a 20% window at anterior and posterior chest images. The regions of interest (ROI) were drawn for the whole heart, lungs, and the mediastinum, and the count per pixel for the heart/mediastinum ratio (H/M), and the count per pixel for the heart/lung (H/L) of 131I-MIBG uptake were calculated. The presence of uptake in the cardiac ROI was interpreted as a negative scan for PD. The H/M > 1.7 and H/L > 1.2 were used for the interpretation by the nuclear physician, but the final decision was more made based on the visual assessment of the presence of activity in the cardiac ROI. The nuclear physician was blind to the clinical diagnosis of the patient but had patient access to perform clinical examination and interview. Throughout the paper, “positive scan” is used for scans indicative of PD with low cardiac uptake, and “negative scan” is used for scans with normal or near-normal cardiac uptake. The initial motor symptoms were defined as follows: rigidity, complaints of stiffness in combination with resistance to passive movement in extremities; tremor, symptoms of uncontrolled shaking in extremities and/or the jaw; and bradykinesia, slowness of spontaneous movement and/or facial expression.

2.3. Statistical analysis

Data analyses were done using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.). A P-value of 0.05 was regarded as statistically significant. Normally distributed continuous variables were presented as mean with standard deviation and non-normally distributed variables described by median (interquartile range boundaries (IQR)). Continuous variables were analyzed using independent group samples t-test if the data were normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were presented as numbers (percentage) and compared by the chi-square and Fisher’s exact test. Eventually, we performed sensitivity and specificity analysis of the MIBG scan for differentiating PD and DIP. Univariate and multivariate regression models (adjusted for potential confounders) were also performed to differentiate the type of Parkinsonism by MIBG result.

2.4. Ethical considerations

This study was approved by the Tehran University of Medical Sciences research and ethics committee based on the Declaration of Helsinki 2013. All of the participants gave written informed consent for using their medical records for research purposes.

3. Results

The demographic and clinical characteristics of DIP and PD patients are presented in Table 1. The mean age of PD and DIP groups were 62.6 ± 5.9 and 51.5 ± 10.8, respectively (P value < 0.001). The male to female ratio was not significantly different between these two groups (P value = 0.675). Regarding the motor manifestation of the DIP, 13 (29.5%) patients had left dominant, 23 (52.3%) had right dominant, and 8 (18.2%) had symmetric symptoms. The mean duration of drug consumption in the DIP group was 52.2 ± 29.4 days, and the mean interval between drug initiation and the onset of the parkinsonism symptoms was 28.5 ± 20.5. The shortest interval was five days due to a combination of Haloperidol (20 mg) and Perphenazine (6 mg), and the longest was regarded to 90 days of taking Risperidone at a dose of 6 mg. 27 (61.4%) patients used typical antipsychotic drugs, 11 (25.0%) patients used atypical antipsychotic drugs, and other 6 (13.6%) patients received both simultaneously. Among 27 patients who were receiving typical antipsychotic drugs, 12 patients were received Trifluoperazine with a daily dose of 6 mg or lower. Among all these patients, DIP was observed for more than 60 days after administration. However, the onset of DIP was <20 days for patients receiving Trifluoperazine at doses above 6 mg. 6 patients have received Haloperidol with doses of 10 or 20 mg. No DIP was noticed with Haloperidol at lower doses. Perphenazine was administered for five patients with doses of 6 or 8 mg, and the interval of DIP was 6 to 8 weeks for these patients.

Moreover, two patients were under Chlorpromazine at doses of 150
and 200 mg, a patient was prescribed Thioridazine at a dose of 20 mg, and Pimozide (4 mg) was administered for the latter. Eleven DIP cases were observed after taking atypical antipsychotic drugs, 9 cases of Risperidone (1 patient), Clozapine (8 patients), Olanzapine plus Quetiapine (1 patient), Aripiprazole (1 patient), Risperidone (1 patient), Quetiapine plus Pentixole Decanoate (20 mg), and two were under Fluphenazine Decanoate (50 mg). Out of 27 patients who used typical antipsychotics, 23 patients had negative MIBG results. However, among patients who used atypical antipsychotics, all of them (n = 11) had negative MIBG results. Also, 2 of 6 patients who received both typical and atypical antipsychotic drugs had positive MIBG. Hence, there was no statistical difference between patients who received different antipsychotic drugs regarding MIBG results (P = 0.154; Table 2). It is to mention that in the later one-year follow-up of these patients, the Parkinsonism symptoms remained in four patients who were under treatment with Levodopa. Also, one patient was later diagnosed with lewy body dementia and is currently receiving appropriate treatment.

The sensitivity and specificity of the MIBG myocardial scintigraphy were 84.4% (CI: 84.0 to 84.8) and 86.4% (CI: 86.0 to 86.7) for the diagnosis of PD, respectively.

Moreover, the univariate and multivariate analysis yielded a significant correlation between positive MIBG scan with PD after adjustment for age and gender. Also, a significant correlation existed between age and PD (Table 3).

## 4. Discussion

Herein, we aimed to define the potential role of the MIBG scan in differentiating the DIP from PD and to determine the sensitivity and the specificity of this scan regarding determining DIP from the PD. This is particularly worthy due to the followed better referral and remarkable difference in the required therapeutic approaches. The results revealed MIBG scan has good accuracy in discriminating DIP from PD.

Differentiating the various types of Parkinsonism from PD is challenging in clinical settings [15]. It has been a while since utilizing MIBG myocardial scintigraphy as a marker to investigate cardiac sympathetic dysfunction [10]. Former works have suggested a decreased heart to mediastinum ratio in patients with PD compared to controls [8,16,17]. The scan has been used to differentiate neurodegenerative PD from other parkinsonian syndromes as well as LBD from AD.

To the best of our knowledge, merely one recent work has applied the MIBG scan to identify the DIP from the PD, in which the MIBG scan was preceded by the $^{123}I$-FP-CIT SPECT (DAT-SPECT) [18]. In our work, however, all participants underwent the MIBG scan, and the results were compared between the two groups. $^{123}I$ was used instead of $^{125}I$, $^{131}I$ labeling, in which $^{131}I$ is more available and $^{123}I$ is more sensitive (sensitivity vs. specificity: $^{123}I$: 82% vs. 79%, $^{131}I$: 82% vs. 79%, respectively) in diagnosis of PD from non-PD parkinsonism. Many clinically available for further discussion on the differences between $^{123}I$ and $^{131}I$ labeled MIBG [19].

The high sensitivity and specificity of using the MIBG scan in distinguishing the PD from other types of Parkinsonism were previously established [17]. Our results indicated 84.4% sensitivity and 86.4% specificity for MIBG scan in differentiating the PD, which is close to the results from similar works [9,17,20]. Also, the competitiveness of the MIBG scan with other nuclear scans is differentiating the neurodegenerative PD [21] from other parkinsonian disorders, emphasizing the considerable utility of the MIBG scan. In this regard, there are few head-to-head comparisons between the MIBG scan and dopamine transporter (DAT) scan to differentiate patients with PD from other parkinsonian syndromes, including DIP. A remarkable report by Statthaki et al. [22] indicates a lower sensitivity but higher specificity for MIBG compared to DAT scan (sensitivity: 82% vs. 100%, specificity: 79% vs. 85%, respectively) in diagnosis of PD from non-PD parkinsonism. Many clinically available MIBG scans show abnormality in DAT scans [23].

Moreover, among DIP patients, statistically more positive MIBG results were observed in patients with a diagnosis of psychotic disease. This observation might be due to differences in the type of prescribed drugs and higher doses of antipsychotics in this group. However, no

### Table 1

Demographic and characteristic features in PD and DIP patients.

|                          | Parkinson’s Disease N = 32 | Drug Induced Parkinsonism N = 44 | P value |
|--------------------------|---------------------------|---------------------------------|---------|
| Age (Years)              | 62.6 ± 5.9                | 51.5 ± 10.8                     | <0.001  |
| Gender (Male)            | 20 (62.5%)                | 24 (54.5%)                      | 0.675   |
| Disease                  |                           | NA                              |         |
| Mood Disorder            | NA                        | 26 (59.1%)                      |         |
| Psychotic Disorder       | NA                        | 18 (40.9%)                      |         |
| Side of Symptom          |                           | NA                              |         |
| Dominance                |                           | NA                              |         |
| Right Dominant           | NA                        | 23 (52.3%)                      |         |
| Left Dominant            | NA                        | 13 (29.5%)                      |         |
| Symmetric                | NA                        | 8 (18.2%)                       |         |
| Duration of Underlying   | 6.2 ± 5.8                 | 4.8 ± 4.3                       | 0.231   |
| Disease (Years)          |                           | NA                              |         |
| Modified Hoehn & Yahr    |                           | NA                              |         |
| Score                    |                           | NA                              |         |
| Type of Antipsychotic    |                           | NA                              |         |
| Drugs                    |                           | NA                              |         |
| Typical                  | NA                        | 27 (61.4%)                      |         |
| Atypical                 | NA                        | 11 (25.0%)                      |         |
| Both                     | NA                        | 6 (13.6%)                       |         |
| MIBG                     |                           | NA                              | <0.001  |
| Negative                 | 5 (15.6%)                 | 38 (86.4%)                      |         |
| Positive                 | 27 (84.4%)                | 6 (13.6%)                       |         |

a Data are presented as mean ± standard deviation or number (%).
association was observed in this group of studies between antipsychotic drugs and the MIBG scan result. However, the prevalence of DIP was higher in those receiving typical antipsychotics compared to the atypical ones. Therefore, further studies would be helpful to clarify the potential impact of drug types.

On the clinical details of our study, it is noteworthy to mention that 26 cases manifested affective psychosis, while 19 manifested primary psychosis. Therefore, the DIP is more prevalent among those with mood disorders compared to primary psychotics. One case manifested DIP without psychotic symptoms after receiving 4 mg of Pimozide for two weeks.

The most delayed response to treatment was also observed after substituting Chlorpromazine for Quetiapine.

Eventually, it is to mention that DIP is generally presented symmetrically, while most of our patients’ manifestations were asymmetrical. As a remarkable, unusual finding, this emphasizes the importance of developing more robust objective diagnostic tools for future works.

Considering that the potential application of MIBG scan in determining the prognosis of the DIP was suggested in a remarkable former study [24], alongside our results, further studies are required to thoroughly examine the applications of MIBG scintigraphy in PD and other types of Parkinsonism syndromes.

Eventually, it is noteworthy that DIP was observed more in cases receiving Risperidone and was not detected in those receiving Clozapine. Also, most patients enrolled in our study were receiving typical antipsychotics, and MIBG scan results yielded statistically insignificant between those under typical and atypical antipsychotics. However, the

Table 2
| MIBG result in different patients’ groups. | P value |
|------------------------------------------|---------|
| MIBG | Positive | Negative | Total | |
| Gender | | | | |
| Male | 0.675 |
| Female | 0.023 |
| Mood Disorder | 0.480 |
| Psychotic Disorder | 0.154 |
| Type of Drug Induced Parkinsonism | |
| Right Dominant | 0.001 |
| Left Dominant | 0.001 |
| Symmetric | 0.001 |
| Type of Antipsychotic Drugs | |
| TYPIC | 0.001 |
| Atypic | 0.001 |
| Both | 0.001 |
| Disease | 0.001 |
| Parkinson’s Disease | 0.001 |
| Drug induced Parkinsonism | 0.001 |

Table 3
| Univariate and multivariate regression model analysis | |
|-----------------------------------------------------|------|
| OR | 95% CI | P Value | OR | 95% CI | P Value |
| Age | 0.842 | 0.771-0.920 | <0.001 | 0.812 | 0.717-0.918 | <0.001 |
| Gender | 2.139 | 0.548-3.519 | <0.001 | 0.489 | 0.374-0.10.971 | 0.412 |
| MIBG | 5.287 | 4.959-5.614 | <0.001 | 85.082 | 12.034-60.1.512 | <0.001 |

MIBG, 123I-metaiodobenzylguanidine OR, odds ratio; CI, confidence interval

Multivariate logistic regression adjusted for “age” and “gender”
potential variations between these medication cases are to be later investigated concerning etiological aspects. Also, although most related studies are conducted using I-123 since this isotope is not available in Iran, I-131 was used as an alternative. The congruency of our results with former related results is intriguing, and further studies are to evaluate this potential utility.

5. Conclusion

In conclusion, our results indicate that the MIBG scan is significantly more positive in the PD group compared to the DIP, which can be potentially due to the cardiac sympathetic dysfunction in the PD patients. Also, with a sensitivity of 84.4% and a specificity of 86.4%, this scan can be used as an acceptable paraclinical aid to differentiate the PD from DIP in complex cases where diagnosis based on mere clinical findings is controversial.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Mahan Shafie: Conceptualization, Methodology, Software, Writing – original draft. Mahsa Mayeli: Conceptualization, Methodology, Software, Writing – original draft. Samira Saeidi: Conceptualization, Resources. Zahra Mirsepassi: Conceptualization, Supervision. Mehrshad Abbasi: Resources, Data curation, Visualization. Melika Shafeghat: Writing – original draft. Vajiheh Aghamollaii: Conceptualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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