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Cardiac ^{123}I-Metaiodobenzylguanidine Scintigraphy in Patients with Parkinson's Disease and Parkinson's Disease with Dementia

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Background: Because patients with idiopathic Parkinson's disease (PD) may exhibit patterns of cognitive impairment, it is difficult to distinguish from patients with Parkinson's disease dementia (PDD). Recently, cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scinti- graphy has been used to help distinguish PD from atypical Parkinsonism. This study investigated the relations between cardiac ^{123}I-MIBG scintigraphy and these diseases.
Methods: Cardiac ^{123}I-MIBG scintigraphy was conducted on 18 patients with PD, 18 patients with PDD and 13 normal controls matched for age, disease duration and severity of symptoms. The heart to mediastinum (H/M) ratio was calculated.
Results: The mean values of H/M ratio were significantly lower for PDD and PD than for normal controls but there was no difference between the disease groups.
Conclusion: Unfortunately, cardiac ^{123}I-MIBG scintigraphy did not distinguish PDD from PD in our study. We suggest further research with larger study populations be done to clarify the use of cardiac ^{123}I-MIBG scintigraphy in differentiating other Lewy body diseases from dementia with PD features.

Key Words: Parkinson's disease, Dementia, ^{123}I-MIBG scintigraphy, Heart to mediastinum ratio

INTRODUCTION

Idiopathic Parkinson's disease (PD) is one of the most common neurodegenerative disorders affecting about 1% of the population over the age of 60[1]. Contrary to the initial assumption that cognitive dysfunction is not an essential feature of the disease, it has become increasingly apparent that patients with PD can have impairments of certain cognitive functions and develop dementia[2,3]. The prevalence of dementia in PD has been reported to range from 2% in early onset cases to 81% in an unselected patient population[2]. Furthermore, PD is associated with a six-fold higher risk of developing dementia when compared to healthy elderly controls[1]. However, because PD patients, even those with mild disease, may exhibit patterns of cognitive impairment, it is difficult to distinguish patients with Parkinson's disease dementia (PDD) from PD patients. Recently, cardiac ^{123}I-metaiodobenzylgua- nidine (MIBG) scintigraphy has been used to distinguish PD from atypical Parkinsonism[4]. Several recent papers reported that PD, diffuse Lewy body disease (DLB) and pure autonomic failure show reduced cardiac 123I-MIBG uptake[5-7]. Suzuki et al.[8] also reported that the mean value of heart to mediastinum (H/M) ratio was significantly lower in patients with DLB than in patients with PD, independent of the Hoehn and Yahr (H&Y) stage. We performed the cardiac ^{123}I-MIBG scintigraphy on PDD and non-dementia PD patients and compared their results to investigate the relationships between cardiac ^{123}I-MIBG scintigraphy and these diseases.

MATERIALS AND METHODS

This study was approved by the local ethics committee. Each patient provided written informed consent for their participation. All subjects were recruited prospectively, and

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the study was conducted between March 2005 and December 2006. The subjects were 18 patients with PD, 18 patients with PDD and 13 age-matched healthy controls free of neurological and cardiovascular abnormalities. There was no significant difference in age and gender among the PD, PDD and control groups. In addition, there was no significant difference in H&Y stage between the disease groups. To evaluate the level of cognitive decline, we performed the Mini-Mental State Examination Korean-version and the expanded version of the Clinical Dementia Rating (CDR) Scale with sum of box (SOB) of CDR[9,10].

The 18 patients with PD were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria and had no previous history of memory impairment nor other cognitive dysfunctions according to the dementia screening questionnaire. The 18 patients with PDD were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria, and the 'Diagnostic and Statistical Manual of Mental Disorders: (DSM-IV). 4th edition' criteria for dementia[11,12]. Excluded were those having marked fluctuating cognition with pronounced variations in attention and alertness and recurrent vivid hallucinations suggesting presence of diffuse Lewy body disease, those taking medications reported to influence cognition and memory, those with any clinical signs of atypical parkinsonism and those who fulfilled the DSM-IV criteria for delirium, amnesic disorder and depressive disorders[12]. We also excluded secondary causes of parkinsonism- Wilson's disease, neuroleptic use and psychiatric diseases that would, in judgment of the investigator, interfere with the safe conduct of this study. Finally, excluded also were patients with a history of neuropathy, previous relevant cardiac disease and any abnormality on routine chest radiography and electrocardiography and those taking medications reported to influence cardiac ^{123}I-MIBG uptake.

Informed consent was obtained from each patient, and the ^{123}I-MIBG scintigraphy was done. Data were collected at 30 minutes (early) and 4 hours (delayed) after injection of 111 MBq of ^{123}I-MIBG using a dual-head camera (Siemens, Hoffman Estates, IL, USA). A static image was obtained with a 128×128 matrix. Regions of interest were manually drawn around the heart, mediastinum and lungs, and tracer uptake was measured to calculate the H/M ratio.

Statistical analysis

Results were expressed as group mean values (SD). Intergroup differences in various variances, including H/M ratio of ^{123}I-MIBG uptake, among PD, PDD patients and control subjects were analysed for statistical significance using the Kruskal-Wallis Test, Wilcoxon Matched-Pairs Signed- Ranks Test or the Mann-Whitney U Test. All tests were performed on the SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA) software program. All p-values less than 0.05 were considered statistically significant.

RESULTS

Table 1 lists the clinical characteristics of the subjects. There was no significant difference in age and gender among the groups. No significant difference in H&Y stage and mean disease duration were seen between PD and PDD patients.

Table 1. Demographic data and general cognitive functions in PD and PDD groups and normal controls

Variables	PD (n=18)	PDD (n=18)	Controls (n=13)	p-value
Male, n	9	7	7	0.690
Mean age (yr)	63.94 (7.69)	68.67 (7.76)	66.94 (5.40)	0.135
Mean eduation (yr)	7.16 (2.91)	4.56 (3.07)	11.72 (4.34)	<0.001
Mean disease duration (mo)	57.62 (29.93)	58.25 (28.33)		0.440
MMSE	28.05 (1.30)	21.50 (4.25)	ND	<0.001
Global CDR score	0.47 (0.12)	0.83 (0.38)	ND	0.002
SOB score of CDR	1.14 (0.48)	4.25 (2.65)	ND	<0.001
H&Y stage	1.86 (0.84)	2.05 (0.75)	ND	0.475

Values are mean (standard deviation).
PD, Parkinson disease; PDD, Parkinson disease dementia; MMSE, mini-mental state examination; CDR, clinical dementia Rating scale; SOB, sum of box, H&Y, Hoehn and Yahr, ND, not done.

However, significant differences between the two disease groups were seen in the MMSE scores, CDR with SOB and level of education. PDD patients showed more severe cognitive impairment and lower level of education than PD patients (Table 1).

In the cardiac ^{123}I-MIBG scintigraphy, the normal mean values of early and delayed H/M ratios in the 13 controls were 2.44±0.37 and 2.47±0.29, respectively. The mean values of early and delayed H/M ratios were 1.43±0.28 and 1.34±0.30 in the patients with PD and 1.51±0.28 and 1.40±0.29 in the patients with PDD. Thus, the mean values of the early and delayed H/M ratios were significantly higher in the control group than in the PD and PDD patients. No significant difference between PD and PDD patients were seen (Fig. 1).

DISCUSSION

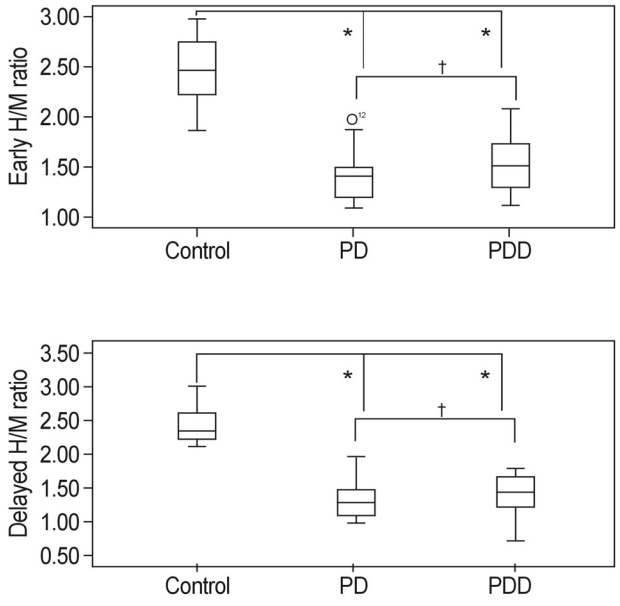

Fig. 1. Comparison of the mediastinum (H/M) ratio of ^{123}I-metaiodobenzylguanidine uptake in the Parkinson's disease (PD), Parkinson's disease dementia (PDD) and normal control groups. The boxplot shows the median value (thick line) and the 25th and 75th percentiles. Early and delayed H/M ratios were compared between PD, PDD and normal control groups with the Kruskal-Wallis Test ($p<0.001$). Early and delayed H/M ratios were also compared between PD and PDD using the Wilcoxon Matched-Pairs Signed-Ranks Test. *Difference seen between the two groups ($p<0.05$), †No difference seen between the two groups ($p>0.05$).

PD, DLB and pure autonomic failure have Lewy bodies as a common pathologic feature and are considered to be 3 phenotypes of a single disorder that may be called Lewy body disease (LBD)[5]. Recent studies have indicated that cardiac ^{123}I-MIBG scintigraphy can detect early disturbance of the sympathetic nervous system in LBD independent of the duration of disease and autonomic failure and provide useful diagnostic information to distinguish LBD from other neurodegenerative disorders5,[13]. Evidence for postganglionic sympathetic nerve involvement in LBD has been provided in recent studies. Histopathologically, Lewy neurites have been detected in the cardiac plexus in all cases of incidental LBD[10]. Orimo et al.[14] also reported that cardiac sympathetic nerves were dramatically depleted, independent of the presence of orthostatic hypotension in LBD patients. Several recent immunohistochemical studies have indicated that tyro- sine hydroxylase-immunoreactive nerve fibers in the heart were markedly decreased in patients with PD, indicating cardiac sympathetic denervation[8,15,16]. Therefore, the reduced uptake of MIBG by the myocardium indicates a weakened capacity of MIBG to enter neuronal tissue. Furthermore,

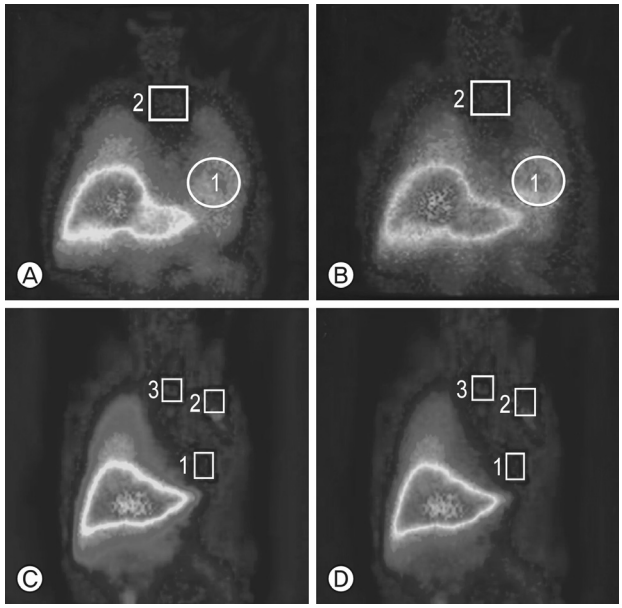

Fig. 2. Cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. All of early (**A**) and delayed images (**B**) reveal normal cardiac ^{123}I-MIBG uptake (the heart to mediastinum [H/M] ratio is 1.94 in the early image and 1.99 in the delayed). On the other hand, figure **C** (early) and **D** (delayed) reveal decreased H/M ratios (H/M ratio is 1.11 in the early image and 1.10 in the delayed) reflecting cardiac sympathetic denervation.

it indicates that the ability of the sympathetic nerves to store MIBG or the amount of sympathetic nerves in the myocardium is reduced in LBD[17]. Our study also showed a significantly lower mean value of H/M ratio in PD and PDD patients with Lewy bodies than in the control subjects. And we assumed that there was no difference between the number of lewy bodies in PD and PDD because we observed no significant difference in ^{123}I-MIBG uptake between PD and PDD.

Dementia is common and affects approximately 40% of PD patients during the course of the disease with the risk for the development of dementia being six times higher than in non-PD age-matched controls[1]. But diagnosis of dementia in patients with PD may be difficult for several reasons. First, apparent impairments in certain cognitive domains may be difficult to differentiate from motor dysfunction. Second, it may be difficult to decide if impairment in activities of daily living is due to cognitive or motor dysfunction[2]. Moreover, PDD and DLB are two common types of dementia of PD with overlapping clinical symptoms, suggesting that they likely represent different points on the LBD spectrum sharing similar underlying neuropathological processes[18,19]. Therefore, distinguishing between PD, PDD and DLB is a very difficult, as well as, important problem. Suzuki et al.[8] recently reported that cardiac sympathetic function in DLB is severely impaired even in the early disease stage and the H/M ratio in DLB is significantly lower than in PD. We saw no difference between the H/M ratios of PD and PDD. According to our results and prior reports, we cautiously assumed that the ^{123}I-MIBG uptake by the myocardium could be significantly lower in patients with DLB than those with PDD, regardless of disease severity. Therefore, according to prior reports, we thought that the uptake of ^{123}I-MIBG is more greatly reduced in DLB than in PDD and PD because of the greater number and wider distribution of Lewy bodies in DLB[8,14].

In conclusion, we carefully conclude that cardiac ^{123}I-MIBG scintigraphy may be helpful in distinguishing DLB from PDD and PD, but not PDD from PD. Future studies with larger numbers of subjects with PDD and DLB are needed to clarify our assumptions and to better delineate the role of cardiac ^{123}I-MIBG scintigraphy in differentiating early stage PDD and DLB among patients with PD features.

SUMMARY

연구배경: 파킨슨병에서 인지기능저하가 흔하게 나타나지만, 파킨슨병 환자에서 치매의 동반 여부를 감별하는 것은 어렵다. 최근에 심장 ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy는 특발성 파킨슨병과 비전형적 파킨슨병들을 구분하는데 사용되고 있다. 따라서 파킨슨병 환자들에서 치매의 동반 여부를 감별하기 위하여 치매 동반여부에 따른 ^{123}I-MIBG scintigraphy 의 결과에 차이가 있는지에 대하여 분석하고자 한다.

방법: 18명의 치매가 동반되지 않은 특발성 파킨슨병 환자, 18명의 치매가 동반된 특발성 파킨슨병 환자 그리고 13명의 정상 대조군에서 심장 ^{123}I-MIBG scintigraphy를 시행하여 심장과 중격동의 흡수 비율(heart to mediastinum [H/M] ratio)을 측정하여 그 차이를 비교 분석하였다.

결과: 모든 특발성 파킨슨병을 가진 환자군에서의 H/M ratio는 정상대조군에 비하여 통계적으로 유의하게 감소된 소견을 보였다. 그러나 치매가 동반된 특발성 파킨슨병군과 치매가 동반되지 않은 특발성 파킨슨병군 사이에서는 H/M ratio의 통계적으로 의미 있는 차이를 보이지 않았다.

고찰: 본 연구에서 ^{123}I-MIBG scintigraphy을 이용한 H/M ratio의 결과로 인하여 특발성 파킨슨병과 정상 대조군에서는 이전 보고들과 마찬가지로 감별이 가능하였으나, 특발성 파킨슨병에서 치매 여부에 따른 H/M ratio의 유의한 차이는 보이지 않았으나, 좀 더 명확한 결론을 내리기 위해서는 향후 더 많은 환자를 대상으로 하는 연구가 필요하리라 생각된다.

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