

Cardiac ¹²³I-MIBG scintigraphy as an outcome-predicting tool for subthalamic nucleus stimulation in Parkinson's disease

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This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a foundation subscribed by Hokuto Hospital, Obihiro, Hokkaido, Japan.

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Summary

Background: ^{123}I -meta-iodobenzylguanidine (MIBG) myocardial scintigraphy is a useful tool for differentiating idiopathic Parkinson's disease (PD) from other parkinsonian syndromes, but its prognostic value in PD has not been established. The objective of this study was to clarify the correlation between cardiac MIBG uptake parameters and the outcome in PD patients subjected to the subthalamic nucleus-stimulation.

METHOD: We enrolled 31 consecutive PD patients and calculated the heart-to-mediastinum ratio (H/M) and washout rate (WR) based on the activity measured at 15 minutes (early phase) and 3 hr (delayed phase) after the intravenous injection of MIBG (111 MBq). Cardinal motor symptoms and activity of daily living (ADL) were assessed on the Unified Parkinson's Disease Rating Scale (UPDRS) and Schwab and England (S-E) ADL scale, before and 3 months after surgery.

Findings: Neither early- nor delayed H/M correlated with any of the preoperative subscores on the UPDRS or S-E, nor with postoperative outcome. On the other hand, increased WR was a positive predictor for postoperative improvement rate on S-E in medication-off state ($p = 0.00003$). Also, WR showed a more faint but significant correlation with preoperative levodopa-responsiveness on S-E ($p = 0.008$).

Conclusion: Our findings suggest that ^{123}I -MIBG scintigraphy in combination with levodopa-responsiveness evaluation may represent a useful tool for prediction of outcomes in patients subjected to STN stimulation.

INTRODUCTION

Continuous high-frequency stimulation of the subthalamic nucleus (STN) is a powerful surgical option for treating the motor complications of Parkinson's disease (PD) [12,16,20,22]. Optimal patients selection is essential for a successful outcome of STN-stimulation [3,27], and ^{123}I -meta-iodobenzylguanidine (MIBG) myocardial scintigraphy may be of great help for obtaining an accurate diagnosis and for decision-making before the surgery [4,17,18,21,23,24,30].

^{123}I -MIBG scintigraphy was originally developed to evaluate cardiac sympathetic innervation and function; it is now used in a variety of cardiac diseases and disorders [24]. The prognostic value of ^{123}I -MIBG parameters in patients with chronic heart failure [9,15,25] has been discussed in the field of cardiology. Aside from its utility in cardiac disease, ^{123}I -MIBG scintigraphy detects depressed myocardial tracer uptake in patients with autonomic failure associated with various neurological diseases [1,6] and cardiac MIBG uptake was found to be significantly depressed in patients with PD and other Lewy body disease in a disease-specific manner. The cardiac sympathetic nerve is thought to be involved in the early disease stage of PD [8,19]. Nagayama et al. [18] demonstrated the strong negative correlation between cardiac MIBG uptake and the Hoehn-Yahr stage in PD, suggesting that Lewy body pathology may be responsible for a low MIBG uptake.

Despite the current acceptance of ^{123}I -MIBG scintigraphy as a useful diagnostic and differentiating tool in PD, its prognostic value has not been established. We examined the correlation between cardiac ^{123}I -MIBG parameters and the treatment outcome in PD patients subjected to STN-stimulation.

METHODS AND MATERIALS

Patients

We enrolled 31 consecutive PD patients who had undergone preoperative cardiac ^{123}I -MIBG scintigraphy between November 2006 and December 2009 (Table 1). All manifested idiopathic PD and all or some of their motor symptoms responded to levodopa. Patients with severe dementia who scored 4 on the Unified Parkinson's Disease Rating Scale (UPDRS)-Part I item 1, patients who scored less than 20 on the Mini-Mental State Examination (MMSE), had uncontrolled major psychiatric symptoms (UPDRS-I, item 2 = 4), or suffered from severe depression (UPDRS-I item 3 = 4) were considered ineligible for surgery [7,12]. The levodopa-equivalent daily dose (LEDD) was computed for each delivered anti-parkinsonian drug, including levodopa, by multiplying the total daily dose of each drug by its potency relative to a standard levodopa dose; the decarboxylase inhibitor (DCI) preparation was assigned the value of 1. The conversion factors were 100 for pergolide, 66.7 for cabergoline, 100 for pramipexole, 10 for bromocriptine, and 33.3 for ropinirole [26]. Surgery was in accordance with good clinical practice and the prior consent of the patients and/or their families was obtained.

^{123}I -MIBG Imaging

The ^{123}I -MIBG was obtained from a commercial source (FUJIFILM RI Pharma Co. Ltd., Japan). Patients in the supine position were injected intravenously with ^{123}I -MIBG (111 MBq) and 15 min (early; E) and 3 h (delayed; D) later, static data were acquired in the anterior view using a dual-head γ -camera (Millennium VG Hawkeye; GE Healthcare) equipped with a medium-energy, general-purpose (MEGP), parallel-hole collimator. Static images on a 256 x 256 matrix were collected for 5 min

with a 20% window centered on 158 keV, corresponding to the ^{123}I photopeak. After acquisition of the static planar images, single photon emission computed tomography (SPECT) images were obtained. The camera was rotated over 360 degrees in 64 views with an acquisition time of 30 s per view. Scans were performed in a 64 x 64 matrix, and the images were reconstructed by ordered subsets-expectation maximization (OSEM) methods.

The heart-to-mediastinum ratio (H/M) was determined from the anterior planar delayed ^{123}I -MIBG image [9,15]. The washout rate (WR) was calculated using the formula

$$\{([H]_E - [M]_E) - ([H]_D - [M]_D) / ([H]_E - [M]_E)\} \times 100 (\%),$$

where [H] equals the mean count per pixel in the left ventricle and [M] the mean count per pixel in the upper mediastinum. We did not correct for time decay in the calculation of WR.

Evaluations

All patients were scored on UPDRS and the Schwab-England (S-E) activity of daily living (ADL) scale. The score after a drug-free period exceeding 12 hr was defined as the practical medication-off state; the score at 1-2 hr after the administration of the usual morning medications as the practical medication-on state. Assessments were performed several days before- and 3 months after surgery by 3 independent observers from our departments.

Surgery

All patients underwent bilateral STN-deep brain stimulation (DBS). We used a magnetic resonance images/microelectrode-guided technique [28,29]. The tentative

target site, determined at coordinate settings, was 2 mm posterior to the midpoint of a line drawn between the anterior commissure (AC)-posterior commissure (PC) line, and 12 mm lateral, and 4 mm ventral to the AC-PC line. Microelectrode recordings were obtained at 1.0-mm sites along the trajectory toward the subthalamic target site to determine the relative physiologic position of the probe. The trajectory that included more than 4 positive recording sites (4.0 mm) was chosen for placement of the DBS electrode (Model 3387 or 3389, Medtronic Inc., Minneapolis, MN, USA).

All patients underwent bilateral procedures in a single operative session. Implantable pulse generators (IPGs) (Soletora, Model 7426, Medtronic) were subcutaneously implanted on the subclavian portion of the chest wall after several days of test-stimulation in 14 of the 31 patients. The other 17 patients underwent simultaneous implantation of DBS electrodes and IPGs.

Most patients were treated with unipolar stimulation using 1 or 2 contacts. The parameters were: frequency, 130-160 Hz; pulse width, 60-90 μ sec, on both sides; stimulation amplitude, 1.5-3.0 V.

Statistics

We individually analyzed 4 parkinsonian motor symptoms, i.e. bradykinesia (UPDRS-III, items 23 to 26; 0 to 32), tremor (UPDRS-III, items 20 and 21; 0 to 28), rigidity (UPDRS-III, item 22; 0 to 20), and axial symptoms (UPDRS-II, items 13 to 15, UPDRS-III, items 27 to 30; 0 to 28)[3,11].

Preoperative levodopa-responsiveness was determined by measuring changes in each score when the patient was in off- and on-medication status (the difference between the on- and off-medication score divided by the off-medication score). The postoperative improvement rate was calculated by determining the

difference between the pre- and postoperative score divided by the preoperative score.

We used the paired Student's t-test to compare parametric pre- and postoperative drug dose data and the Wilcoxon signed-rank test to compare UPDRS subscores and the S-E scale before and after surgery. All data are expressed as the mean \pm standard deviation (SD). To determine which preoperative clinical characteristics (age, duration of disease, and neuropsychiatric-, motor-, complication of therapy-, and ADL subscores) were related to the ^{123}I -MIBG scintigraphy parameters we performed univariate analysis. Values of $p < 0.01$ were considered as statistically significant.

RESULTS

Correlation between ^{123}I -MIBG scintigraphy parameters and preoperative clinical characteristics

None of the patients was treated with reserpine or tricyclic antidepressants. An association with chronic heart failure was excluded based on clinical symptoms and echocardiography (ejection fraction > 50%).

While the normal range (mean \pm SD) of E- and D-H/M in our institute is 2.78 ± 0.32 and 3.17 ± 0.29 , respectively, those of our patients were 1.53 ± 0.31 and 1.31 ± 0.37 , respectively. WR (%) was 62.37 ± 21.23 (normal range: 15.2-44.4). Neither E- nor D-H/M correlated with the patient age, the disease duration, or preoperative subscores on the UPDRS or S-E ($p > 0.01$). However, there was a significant correlation between WR and the S-E score in the medication-off state ($p = 0.0096$) and between WR and levodopa-responsiveness on S-E ($p = 0.0075$)(Fig. 1A).

Postoperative status

Postoperatively, none of the 31 patients exhibited permanent adverse effects such as motor weakness, sensory disturbance, oculomotor palsy, or cognitive decline. Transient effects were effectively treated by modifying their anti-parkinsonian medications, or by changing the DBS parameters. There were no infectious complications.

The anti-parkinsonian drug doses could be reduced significantly as the parkinsonian symptoms were ameliorated by chronic STN-DBS. At 3 months after the procedure, there was a significant reduction in the mean dosage of levodopa/DCI and LEDD ($p < 0.001$, Table 2).

Compared to the preoperative baseline, at 3 months postoperatively, the

UPDRS-I, II-, III-, and IV scores in both the medication-on and -off state were significantly reduced ($p < 0.0001$), all aspects of motor symptoms including bradykinesia, tremor, rigidity, and axial symptoms were significantly improved as were the S-E scores in both the on- and off-medication state ($p < 0.001$, Table 2).

Correlation between ^{123}I -MIBG scintigraphy parameters and postoperative scores

There was a significant correlation between preoperative levodopa-responsiveness on S-E and the postoperative improvement rate in the off-medication state ($p < 0.0000001$, data not shown).

While E- and D-H/M and WR were not correlated with any postoperative UPDRS subscores or S-E ($p > 0.01$), increased WR was a positive predictor of the postoperative improvement rate on S-E in the medication-off state ($p = 0.000031$)(Fig. 1B).

DISCUSSION

The disease process of PD as measured by neuronal degeneration and Lewy body and neuritic pathology is widespread in the central and peripheral nervous systems [2]. As many of these non-nigral sites also produce clinical signs and symptoms, Langston [13] proposed that PD might be better viewed as a “centrosympathomyenteric neuronopathy”. The Lewy body-type degeneration in the cardiac plexus is observed in almost all patients with incidental Lewy body disease as well as in patients with PD [8], and the number of sympathetic nerve fibers was markedly decreased in all the PD patients regardless of the presence or absence of orthostatic hypotension [19]. These findings suggest the involvement of the cardiac sympathetic nerve in the preclinical disease stage [8,19], consistent with the reduction in cardiac MIBG uptake in the early stage of PD.

According to Taki et al. [24] MIBG imaging represents an indicator of the presence of PD rather than its severity, while Nagayama et al. [18] demonstrated the negative correlation between cardiac MIBG uptake and the Hoehn-Yahr stage. We found that the relative change in MIBG uptake at the early- and delayed phase (WR) was a significant predictor of the relative improvement (rate) of postoperative ADL. It has been suggested that early MIBG uptake reflects the integrity and distribution of the presynaptic sympathetic system, and that MIBG washout reflects the presynaptic functional status or tone of the sympathetic nervous system [24]. Increased MIBG washout may indicate an increase in the norepinephrine turnover. We also found that WR of MIBG significantly correlated with the levodopa-responsiveness of ADL, known to predict a favorable response to bilateral STN-stimulation [3,11]. These observations raise the hypothesis that the norepinephrine elimination rate at the myocardial sympathetic nerve endings may inversely parallel the dopamine-preserving capacity in

the striatum.

Ethnic characteristics may underlie the observation that many Japanese patients treated with lower-dose antiparkinsonian drugs manifest various motor and/or non-motor side effects [10,28,29]. Consequently, their preoperative UPDRS subscores in the medication-on state may not reflect the best obtainable scores in that state. We therefore cannot rule out the possibility that we evaluated preoperative ADL at an insufficient dose of levodopa and that STN stimulation elicited symptom improvement by acting as an “additional dopamine” [5,14,16]. Indeed, as demonstrated in the present study, the scores for ADL and motor function were significantly improved by STN stimulation, not only in the off-, but also in the on-medication state. In such instances, the postoperative improvement rate may often be underestimated before surgery. In combination with levodopa-responsiveness evaluation, WR of MIBG is considered to be very useful to predict postoperative outcome.

Contrary to our expectations, WR of MIBG was not correlated with the postoperative improvement rate of UPDRS subscores (data not shown). A gross myocardial sympathetic function measure based on ^{123}I -MIBG scintigraphy may respond better to the overall daily activities expressed by S-E than individual UPDRS subscores. Furthermore, there may be some methodological limitations in conventional calculating formula that we adopted for improving rate of UPDRS. As discussed above, we speculate that reduction rate of ^{123}I -MIBG activity may parallel to wearing-off phenomenon. If so, we should assess levodopa-responsiveness (as well as postoperative improvement) by measuring the reduction rate of scores in the worse state. However, in the present analysis using the conventional formula, those were calculated by the reduction rate of UPDRS subscores in the better state on the basis of

the worse state. More adequate method is needed to clarify relationship between cardiac ^{123}I -MIBG parameters and UPDRS subscores.

CONCLUSION

In PD patients who underwent STN stimulation, we found a statistically significant correlation between the WR of myocardial MIBG and the levodopa-responsiveness in ADL scale. Myocardial norepinephrine turnover might parallel to preserving capacity of the basal ganglia dopamine system. The present study also demonstrated a close relationship between WR of MIBG and postoperative improvement rate of ADL, suggesting that ¹²³I-MIBG scintigraphy in combination with levodopa-responsiveness evaluation may represent a useful tool for prediction of outcomes in patients subjected to STN stimulation.

Acknowledgement

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a foundation subscribed by Hokuto Hospital, Obihiro, Hokkaido, Japan.

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Figure Legend

Figure 1. Scatter plot and linear regression analysis (95% confidence interval) showing the relationship between WR and preoperative levodopa-responsiveness of S-E (A), and between WR and postoperative improving rate of S-E in off-medication (B). There is a statistically significant correlation (A; $p < 0.01$, B; $p < 0.0001$).