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Imaging-based differential diagnosis between multiple system atrophy and Parkinson's disease

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ABSTRACT

There are many tools for differentiating between multiple system atrophy with predominant parkinsonian features (MSA-P) and Parkinson's disease (PD). These include middle cerebellar peduncle (MCP) width, apparent diffusion coefficient (ADC) value of the putamen and cerebellum, and ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy images. We aimed to directly compare the above-mentioned methods, and to determine the optimal tool for differential diagnosis. Eleven patients with MSA-P and 36 patients with PD were enrolled. Of these, 7 patients with MSA-P and 14 patients with PD were chosen as background-matched subjects. We measured MCP width, ADC value of the putamen and cerebellum, and MIBG myocardial scintigraphy images. Area under curve (AUC) of receiver operating characteristic (ROC) was assessed to compare the above-mentioned methods. MCP width and ADC value of the putamen may be helpful for differentiating between MSA-P and PD relative to other methods in background-matched patients (MCP, AUC = 0.95; putamen ADC, AUC = 0.88; cerebellar ADC, AUC = 0.70; MIBG, AUC = 0.78). Similar AUCs were seen in all patients with different backgrounds. Our findings suggested that MCP width and ADC value of the putamen could be superior to ADC value of the cerebellum and MIBG uptake for differentiating between MSA-P and PD.

1. Introduction

It is difficult to distinguish idiopathic Parkinson's disease (PD) at the early stage from other parkinsonian syndromes including multiple system atrophy with predominant parkinsonian features (MSA-P) and progressive supranuclear palsy (PSP) [1–4]. To address this issue, many objective methods have been tested for the differential diagnosis, such as proteins in cerebrospinal fluid (CSF) [5,6], magnetic resonance imaging (MRI) and positron emission tomography (PET) [7–18]. PET could be a reliable tool for the differential diagnosis of parkinsonian syndromes [15,17,18], although the use of PET was limited due to radiation and invasive properties. In contrast, MRI can be performed without radiation or invasion, and MRI sequences permit examination of size and water diffusivity in targeted regions. Volume, area, width and apparent diffusion coefficient (ADC) have been utilized to make a differential diagnosis in the putamen, cerebellum and middle cerebellar peduncle (MCP) [7–16]. These methods provided relatively high sensitivity and specificity. Furthermore, ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy images might be helpful for the differential diagnosis, but results of this method were heterogeneous [19]. In particular, several studies reported the low specificity of MIBG myocardial scintigraphy [20–22]. These findings have raised the question of which method is best for differential diagnosis between parkinsonian syndromes. To the best of our knowledge, however, there have been no studies which directly compared all of the above-mentioned methods. We aimed to directly compare the above-mentioned methods including MCP width, ADC value of the putamen and cerebellum, and MIBG myocardial scintigraphy, and to determine the optimal tool for differential diagnosis.

2. Methods

2.1. Subjects

All patients were recruited from the Department of Neurology of the Tokushima University Hospital over the period April 2005–April 2013. The screening criteria were as follows: (1) patients diagnosed PD or MSA-P according to widely accepted criteria [1,23]; (2) patients who underwent both MRI and MIBG; and (3) no family history of PD or MSA-P. Of these, we selected patients with images from 3.0-tesla (-T) MRI and disease duration <4.5 years were to minimize the effects of

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machine and disease progression. Finally, 7 MSA-P and 14 PD patients were included in the present study and were background-matched. Furthermore, all data were analyzed regardless of MRI or disease duration (i.e., 11 MSA-P and 36 PD patients). Fig. 1 shows the flow diagram for the present study. We evaluated age at scan, sex, age at onset, disease duration and Hohen–Yahr stage (H–Y). Disease duration was defined as the duration from the onset of motor symptoms to the time of MRI or MIBG scan. All patients were followed up for at least three years. Clinical data are summarized in Table 1. Informed consent was obtained from all participants, and the study protocol was approved by the local ethical committee.

2.2. MRI acquisition, image processing and MIBG

Images were acquired using a 1.5- or 3.0-T MRI (GE, Milwaukee, WI) with a standard head coil. The DWI protocol included the following parameters: b value, 1000 s/mm^2; TE, 89.8 ms (79.8 ms for 1.5-T MRI); TR, 10 s; FOV, 240 mm; matrix, 128 × 128; flip angle, 90; slice thickness, 6 mm; and slice gap, 1.5 mm. ADC maps were derived from DWI using an in-house program based on the following equation: ADC = [ln(S0) − ln(S1)] / b, where b denotes b-value of 1000 and S0 and Sb denote the signal intensities for each b value (i.e., b = 0 or b = 1000). The b0 images were registered to the MNI-152 image template (2 × 2 × 2 mm^3) using a 12-parameter affine transformation and the resulting transformation was then applied to the ADC maps to register them to MNI space [24]. The volume of interests (VOI) for ADC analysis were generated with WFU Pickatlas [25]. Each VOI with a radius of 2 mm was centered at x = ±28, y = −7, z = 0 and x = ±27, y = −62, z = −32 for putamen and cerebellum, respectively (Supplementary Fig. 1). These VOIs allowed for automatic measurement of ADC value of the putamen and cerebellum in standard space. The detailed method for measurement of MCP width was described in a previous study [16]. The MIBG myocardial scintigraphy images in early and delayed phases were obtained 15 min and 3–4 h after injection, respectively. The heart to mediastinum ratio was considered as the MIBG uptake.

2.3. Statistics

A two-tailed unpaired Student's *t*-test was used for continuous variables, and chi square test or Fisher's exact test was used for categorical variables. Findings were considered as significant for $P < 0.05$. These analyses were conducted using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY). Furthermore, receiver operating characteristic (ROC) curves were generated, and each area under curve (AUC) was computed using R software (http://www.r-project.org/).

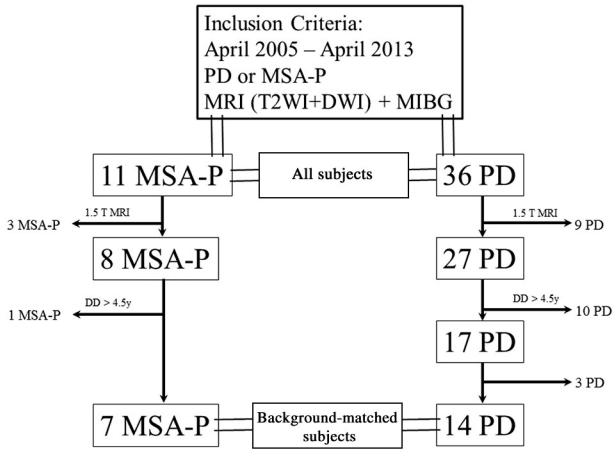

Fig. 1. Flow diagram for the present study. The diagram depicts the flow of inclusion and exclusion of subjects. Data from all or background-matched subjects were analyzed. Abbreviations: DD, disease duration; DWI, diffusion weighted images; MIBG, ^{123}I-metaiodobenzylguanidine myocardial scintigraphy; MRI, magnetic resonance imaging; MSA-P, multiple system atrophy with predominant parkinsonian features; PD, Parkinson's disease; T, tesla; T2WI, T2 weighted images; y, years.

3. Results

In terms of background-matched subjects, MCP width and ADC value of the putamen showed higher AUC compared with the other methods (MCP width, AUC = 0.95, 95% confidence interval (CI) 0.85 to 1.00, *P* value 0.001; ADC value of the putamen, AUC = 0.88, 95% CI 0.71 to 1.00, *P* value 0.006; ADC value of the cerebellum, AUC = 0.70, 95% CI 0.44 to 0.97, *P* value 0.136; MIBG uptake in the early phase, AUC = 0.76, 95% CI 0.55 to 0.98, *P* value 0.057; MIBG uptake in the delayed phase, AUC = 0.78, 95% CI 0.56 to 1.00, *P* value 0.040; Supplementary Table 1, Fig. 2). That said, these two approaches could be helpful for differential diagnosis between MSA-P and PD relative to other methods. Similar AUCs were observed to those from background-matched data even though all subjects with different backgrounds (i.e., 1.5-T vs. 3.0-T MRI, disease duration >4.5 years vs. disease duration <4.5 years) were analyzed (Supplementary Table 1, Fig. 3). Intriguingly, cut-off values were almost the same as those from the background-matched data (Supplementary Table 1). No adverse events were observed in the present study.

4. Discussion

The area under the ROC curve suggested that MCP width and ADC value of the putamen could be superior to ADC value of the cerebellum and MIBG uptake for differentiating between MSA-P and PD. MCP width was reported to exhibit high sensitivity and specificity, which was compatible with our results [13,16,26]. For ADC value of the putamen, results were heterogeneous across studies even though high sensitivity and specificity were demonstrated in the present study [7–9,11,12,27]. Whole putamen VOI/ROI tended to generate an unremarkable ADC difference between MSA-P and PD [27]. In contrast, posterior dorsolateral putamen VOI/ROI contributed to a relatively clear ADC difference between MSA-P and PD maybe because this region was considered as motor putamen [7,9,11,12]. We applied the VOIs in posterior dorsolateral putamen in standard space, although previous studies used ROI/VOI in native space. VOI in standard space allowed for automatic measurement of putamen ADC value without bias, and providing objective results.

In contrast, MIBG uptake and cerebellar ADC value resulted in lower sensitivity and specificity than those of the other methods in the present study. The results of MIBG uptake have been heterogeneous for the differential diagnosis of parkinsonian syndromes [19], but the cause of heterogeneity remains unknown. Further meta-analysis is required to determine the cause of heterogeneity. Mean diffusivity (MD) of the cerebellar hemisphere, derived from DWI, was reported to be elevated in MSA relative to PD [28], whereas another study showed no significant difference in MD between MSA and PD [13]. Our study suggested that ADC value of the cerebellum was less helpful compared with ADC value of the putamen and MCP width. As few studies have examined ADC or MD of the cerebellum for the differential diagnosis, the utility of these values remains controversial.

Direct comparison between ADC value of the putamen and MIBG uptake indicated the superiority of MRI over MIBG uptake [12,21]. Our findings were compatible with previous studies. In addition, MCP width derived from MRI showed the optimal AUC among the methods used in the present study. Collectively, MRI without invasion or radiation is considered as the first option for the differential diagnosis of parkinsonian syndromes.

As previously reported, putamen volumetry is another candidate which can help in differentiating between MSA-P and PD [14]. A