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The effect of tremor onset on middle cerebellar peduncle of Parkinson's disease

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ABSTRACT

The majority of studies of Parkinson's disease (PD) focused on basal ganglia initially; however, accumulating evidence suggests cerebellar involvement in pathophysiology. We aimed to investigate the effects of tremor onset on middle cerebellar peduncle (MCP) width of PD patients and of disease duration on differential diagnosis. We measured MCP width of 81 PD, 34 multiple system atrophy (MSA) and 16 normal controls, using MRI. A meta-analysis was performed including two previous and the present studies. We carried out correlation analysis between disease duration and MCP width separately in subgroup of PD with or without tremor onset. Receiver operating characteristic curves were analyzed. Our meta-analysis indicated that MCP width was significantly smaller in MSA relative to PD with homogeneous studies. There was significant correlation between disease duration and MCP width in PD without tremor onset. In contrast, there was no correlation observed in PD with tremor onset. Subclassification according to disease duration showed improved area under curve of PD vs. MSA with predominant parkinsonian features. MCP width could be a valuable tool for differential diagnosis. Our finding suggested that MCP was impaired in advanced stage of PD without tremor onset as part of the abnormality of the cerebellar system.

1. Introduction

Parkinson's disease (PD) is characterized by tremor, rigidity, bradykinesia/akinesia and postural instability caused by dopaminergic neuronal loss in the substantia nigra pars compacta. The majority of studies focused on basal ganglia in PD patients initially, because dopamine is considered to be essential to maintain basal ganglia function. However, accumulating evidence suggests cerebellar involvement in pathophysiology of PD [1].

The pathophysiology of tremor appeared to be different from other parkinsonian symptoms because the response of tremor to dopaminergic agents was less certain than bradykinesia [2]. Positron emission tomography (PET) indicated that striatal dopamine deficiency most closely correlated with bradykinesia and rigidity rather than resting tremor [3,4]. The severity of PD tremor was reported to correlate with median raphe 5-HT_{1A} receptor binding [5]. Furthermore, functional MRI study raised the possibility that increased interactions between the basal ganglia and a distinct cerebellothalamic circuit mediate the occurrence of resting tremor [6]. These findings suggested the different effect of tremor from other parkinsonian symptoms, and that cerebellum played a key role in pathophysiology of tremor in cooperation with the basal ganglia. Indeed, subthalamic neurons project to pontine nucleus, and this nucleus provides projections to cerebellar cortex through middle cerebellar peduncle (MCP) [7]. In this context, we hypothesized that the MCP width was different between PD patients with and without tremor onset.

On the other hand, the measurement of MCP width allowed for differential diagnosis between PD and multiple system atrophy (MSA) or MSA with predominant parkinsonian features (MSA-P) [8–11]. However, these studies included the patients with long disease duration. The previous meta-analysis of putamine volumetry reported that disease duration contributed to heterogeneity of PD [12]. Therefore, we assumed that disease duration correction could improve sensitivity and specificity of differential diagnosis between PD and MSA or MSA-P using MCP width.

In this study, we aimed to investigate the effects of tremor onset on MCP width of PD patients and of disease duration on differential diagnosis.

2. Methods

2.1. Subjects

All participants were recruited through the Department of Neurology in Tokushima University Hospital in Tokushima over the period April

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Table 1
Characteristics of participants in this study.

Categorized by disease duration	Subgroup	Number	Sex (M/F)	Age −year	Disease duration −year	H–Y	MCP width −mm
	NC	16	6/10	62.6 ± 13.9	NA	NA	16.9 ± 0.94
<4 years	PD with tremor onset	32	15/17	64.1 ± 9.04	2.0 ± 2.09	1.8 ± 0.59	16.8 ± 1.16
	PD without tremor onset	17	11/6	59.7 ± 9.76	1.7 ± 1.32	1.5 ± 0.51	16.9 ± 1.13
	MSA-P	6	2/4	60.5 ± 9.05	2.0 ± 1.42	2.7 ± 0.52	14.9 ± 0.81
	MSA-C	21	11/10	61.7 ± 6.24	2.0 ± 0.97	NA	11.2 ± 2.6
>4 years	PD with tremor onset	16	7/9	65.8 ± 5.19	9.7 ± 4.8	2.9 ± 0.59	17.0 ± 1.1
	PD without tremor onset	16	5/11	58.3 ± 8.42	6.6 ± 2.6	2.8 ± 0.52	15.7 ± 0.75
	MSA-P	2	1/1	60.6 ± 3.39	7.1 ± 0.15	3.8 ± 0.36	11.1 ± 5.4
	MSA-C	5	4/1	63.4 ± 10.0	4.8 ± 0.51	NA	11.7 ± 3.2

Abbreviations: H–Y, Hoehn–Yahr stage; MCP, middle cerebellar peduncle; MSA-C, multiple system atrophy with predominant cerebellar ataxia; MSA-P, multiple system atrophy with predominant parkinsonian features; NA, not available; PD, Parkinson's disease.

2005–March 2011. We evaluated age at scan, sex, family history, onset form, age at onset, disease duration and Hohen–Yahr stage (H–Y). The definition of disease duration was from the onset of motor symptom to the time of MRI scan. The subjects with family history of PD or MSA were excluded in order to avoid confounding due to genetic effects. Eighty-one subjects met the United Kingdom PD Brain criteria [13]: 32 PD with tremor onset and disease duration <4 years, 17 PD without tremor onset and disease duration <4 years, 16 PD with tremor onset and disease duration >4 years and 16 PD without tremor onset and disease duration >4 years. We defined PD patients whose motor symptom started with tremor as PD with tremor onset. Thirty-four subjects met MSA consensus [14]: 6 MSA-P with disease duration <4 years, 21 MSA-C with disease duration <4 years, 2 MSA-P with disease duration >4 years and 5 MSA-C with disease duration >4 years. Subjects of disease groups were divided into two subgroups according to disease duration of 4 years because the previous meta-analysis of putamen volumetry demonstrated that disease duration <4 years for PD was critical for homogeneity [12]. Moreover, 16 age-matched normal controls (NC) were enrolled in this study. Demographic and clinical data from these subjects are provided in Table 1. Informed consent was obtained from all participants under protocols approved by the local ethical committee.

2.2. MRI acquisition and MCP measurement

The present study was performed using a 3.0 tesla MRI (GE, Milwaukee, WI) with a standard head coil. Axial T2-weighted images were acquired under condition of 2D-FSE, TR = 5000 ms, TE = 100 ms, flip angle = 90°, FOV = 240 mm and thickness = 6 mm. For the MCP width, the same definition as previous paper was applied to the present study [10]. The average of maximal widths in right and left MCP was used as "MCP width" for further analyses. MCP measurement was performed by two investigators (W.S. and N.M.) who were blinded to the diagnosis using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

2.3. Meta-analysis

In terms of search strategy and study selection, inclusion criteria in this study were: (1) measurement of MCP width using MRI; (2) comparisons between PD and MSA; (3) classification of groups according to internationally agreed consensus criteria; (4) written in English. We performed a systematic search of PubMed using the following syntax: ("multiple system atrophy" or "MSA") and ("magnetic resonance imaging" or "MRI") and ("middle cerebellar peduncle" or "MCP"). This search was performed in October 2014, and yielded in 29 papers. We retrieved 6 full articles based on title and abstract review. Of 6 studies, 4 were excluded for the following reasons: subjects were overlapped with other previous reports (2 papers), no value of MCP width (1 paper) or we cannot find mean and standard deviation of MCP width (1 paper). One study showed only mean and range, and we estimated standard deviation of PD and MSA using the formula [15]. Two studies and the present study were finally included in the meta-analysis [8,9]. Two authors double-checked the inclusion criteria of the identified studies (W.S. and N.M.). The corresponding authors were contacted in order to obtain essential data if their results were not explicitly stated in the papers or were only represented graphically. Two authors independently extracted data and checked each other (W.S. and N.M.). Any discrepancy was resolved by discussion.

For data synthesis, random-effects model was applied to the present meta-analysis, and standardized mean difference (SMD) was employed to combine each effect (Hedge's g). Heterogeneity was assessed by P value of χ^2 statistics and I^2. The amount of heterogeneity for each outcome was calculated based on DerSimonian–Laird model, with τ as an estimate for the standard deviation (SD) of the underlying true outcomes across studies. Furthermore, we performed a sensitivity analysis to explore the robustness of our findings. Analyses were performed using Review Manager (RevMan 5.2) for Windows (http://ims.cochrane.org/revman).

Publication bias was assessed by visual inspection of funnel plot asymmetry and applying the Egger's linear regression test, which examines whether the intercept deviates significantly from zero in a

Table 2
Characteristics of studies included in this meta-analysis of measurement of middle cerebellar peduncle.

Study	Scanner	Tesla	Image	View	Group	Sample size	Male (Female)	Age −year	Disease Duration −year	H–Y
Gama 2010	GE	1.5	T2WI	Axial	MSA	13	4 (9)	61.2 ± 3.94	4.7 ± 2.73	4.5 ± 0.66
					PD	16	7 (9)	64.0 ± 11.2	6.0 ± 3.66	2.5 ± 0.74
Nicoletti 2006	GE	1.5	T1WI	Sagittal	MSA	16	4 (12)	63.9 ± 5.56	5.1 ± 3.38	4 (3–5)
					PD	26	15 (11)	65.3 ± 7.48	5.9 ± 6.46	2.75 (1–5)
The present study	GE	3.0	T2WI	Axial	MSA	34	18 (16)	61.7 ± 7.0	2.7 ± 1.79	2.9 ± 0.68
					PD	81	38 (43)	62.4 ± 8.8	4.4 ± 4.27	2.1 ± 0.8

Abbreviations: H–Y, Hoehn–Yahr stage; MSA, multiple system atrophy; MSA-P, multiple system atrophy with predominant parkinsonian features; PD, Parkinson's disease; T1WI, T1-weighted image; T2WI, T2-weighted image. ¶: This value was derived from only MSA-P patients.