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The difference of apparent diffusion coefficient in the middle cerebellar peduncle among parkinsonian syndromes: Evidence from a meta-analysis

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ABSTRACT

The measurement of middle cerebellar peduncle (MCP) width allows for differential diagnosis between Parkinson's disease (PD) and multiple system atrophy with predominant parkinsonian features (MSA-P). However, it remains controversial whether apparent diffusion coefficient (ADC) value in the MCP of MSA-P is elevated or not. In the present study, we aimed to assess the usefulness of ADC value in the MCP for differential diagnosis between PD and MSA-P. An on-line literature search yielded 5 eligible studies. We expressed between-group difference of ADC value as the standardized mean difference (SMD). The proportion of variation due to heterogeneity was computed and expressed as I^2. ADC in the MCP of MSA-P was significantly increased compared with PD with heterogeneous studies ($P = 0.0007$, $I^2 = 81\%$). A meta-regression analysis of MSA-P was conducted for "UPDRS III", and revealed a significant correlation between UPDRS III and SMD ($P = 0.01$). Our meta-regression analysis has clarified the contribution of severity of MSA-P to heterogeneity of the included studies for ADC in the MCP. This finding raised the possibility that ADC in the MCP depended on severity of MSA-P, and less severe patients with MSA-P should be mainly enrolled in future study to assess the ability for differential diagnostic tool.

1. Introduction

Quite a few patients misdiagnosed as having idiopathic Parkinson's disease (PD) actually have multiple system atrophy (MSA) or progressive supranuclear palsy (PSP), the most common atypical parkinsonian syndromes [1]. The reliable diagnostic approach has been required to distinguish PD, MSA and PSP.

A candidate region of interest is middle cerebellar peduncle (MCP). MCP mainly consists of input fibers into cerebellar cortex. Of interest, subthalamic neurons project to pontine nucleus, and this nucleus provides projections to cerebellar cortex through MCP [2]. That is, MCP connects basal ganglia network with cerebellar cortex.

The measurement of the MCP width was useful for differential diagnosis between PD and MSA or MSA with predominant parkinsonian features (MSA-P) [3–7]. Apparent diffusion coefficient (ADC) is a measure of magnitude of water diffusion, and increased in a neurodegenerative lesion. Several studies reported that MSA showed reduced value of ADC of the MCP compared with PD [8–12]. However, difference of ADC value between MSA and PD appeared heterogeneous, and the cause of heterogeneity remains unknown [8–12].

A meta-analysis allows for computing an estimate of the effect size for each study, which produces a summary effect to elucidate the underlying overall effect of disease across published studies. Previous meta-analyses of several biomarkers have revealed reduced volume of the putamen in MSA compared with PD, reduced alpha-synuclein concentration in cerebrospinal fluid (CSF) in PD and MSA compared with PSP, and increased neurofilament light chain concentration in CSF in MSA and PSP compared with PD [13–15]. Moreover, if significant heterogeneity is seen in the included studies, meta-regression and subgroup analyses would help to determine the cause of heterogeneity [16].

In this study, we aimed to establish robust evidence of elevated value of ADC of the MCP in MSA compared with PD and PSP, and to detect the cause of heterogeneity using a meta-analysis, subgroup analysis and meta-regression analysis.

2. Methods

2.1. Search strategies and study selection

Inclusion criteria in this study were: (1) measurement of regional ADC of the MCP; (2) comparisons between PD and atypical parkinsonian syndromes; (3) diagnosis and classification of groups according to internationally agreed consensus criteria including the UK Parkinson's Disease Society Brain Bank criteria, Calne's criteria for PD

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[17], Gilman's criteria for MSA-P [18] and the report of the National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy International Workshop [19]; and (4) written in English. We performed a systematic search of PubMed, Cochrane library and web of science using the following syntax: ("middle cerebellar peduncle" or "MCP") and ("magnetic resonance imaging" or "MRI") and ("Parkinson's disease" or "PD"); ("middle cerebellar peduncle" or "MCP") and ("magnetic resonance imaging" or "MRI") and ("multiple system atrophy" or "MSA"); ("middle cerebellar peduncle" or "MCP") and ("magnetic resonance imaging" or "MRI") and ("progressive supranuclear palsy" or "PSP"). This search was performed in March 2015, and yielded 43 papers. We retrieved 7 full articles based on title and abstract review. Of 7 studies, 2 were excluded because there was no value of ADC of the MCP. Further information was sought through a manual search of references from recent reviews and relevant published original papers, but no additional studies were found. Five studies were finally included in the meta-analysis [8–12]. Two authors (WS and NM) double-checked the inclusion criteria of the identified studies. Two authors (WS and NM) independently extracted data and checked each other. Any discrepancy was resolved by discussion.

2.2. Data synthesis and statistics

Random-effects models were employed for the meta-analysis. 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, which describes the proportion of variability in the effect estimates due to heterogeneity. 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. We planned to perform a subgroup analysis and meta-regression analysis to explore the cause of heterogeneity if significant heterogeneity was detected between studies. Furthermore, we performed a sensitivity analysis to explore the robustness of our findings.

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 regression of the standardized effect against inverse of the standard error. All analyses were performed using the library of "meta" and "metafor" in R software (http://www.r-project.org/), and Review Manager (RevMan 5.2) for Windows (http://ims.cochrane.org/revman).

3. Results

3.1. Study characteristics

Supporting Fig. 1 depicted the flow chart for the process of selecting eligible studies. Five studies of ADC in the MCP satisfied our inclusion criteria (114 controls, 114 PD patients, 57 MSA-P, 76 PSP). The pooled mean baseline characteristics were as follows: age (range 57.3–74.6 years), male (range 4–41), female (range 3–41), disease duration (range 2.0–13.3) years, Hoehn-Yahr stage (HY) (range 2.0–4.0), and unified Parkinson's disease rating scale III (UPDRS III) (range 16.7–48.0). Three of five scans were acquired on a 1.5-T GE machine, one of five scans was acquired on a 3.0-T GE machine, and the last study used 1.5-T and 3.0-T machines. Four of five studies used b value of 1000, and the other used b value of 900. The number of directions is 3

Table 1
Characteristics of studies included in this meta-analysis.

Study name	Scanner	Tesla	b value	The number of directions	Group	Sample size	ADC value ($\times 10^{-3}$ mm^2/s) mean ± SD	Age mean ± SD (yr)	Male (female)	Disease duration mean ± SD (yr)	HY mean ± SD	UPDRS III mean ± SD
Chung 2009	GE	1.5	1000	3	NC	10	0.75 ± 0.06	62.1 ± 9.77	4 (6)			
					PD	12	0.69 ± 0.08	65.7 ± 10.88	5 (7)	2.5 ± 1.84	2.0 ± 0.78	32.7 ± 15.24
					MSA-P	10	0.98 ± 0.17	63.6 ± 8.25	5 (5)	2.0 ± 1.07	2.5 ± 0.97	30.3 ± 12.26
Nicoletti 2006	GE	1.5	900	3	NC	15	0.81 (0.68–0.85)[a]	67.5 ± 6.0	5 (10)			
					PD	16	0.79 (0.73–0.85)[a]	61.0 ± 7.7	9 (7)	7.5 ± 5.8	2.25 (1–3)[a]	23.5 (12–40)[a]
					MSA-P	16	0.93 (0.89–1.17)[a]	64.7 ± 5.1	4 (12)	4.9 ± 4.0	3.5 (3–5)[a]	42.2 (29–80)[a]
					PSP	16	0.82 (0.71–0.85)[a]	70.7 ± 7.8	13 (3)	3.3 ± 2.5	4.0 (3–5)[a]	48 (3–90.5)[a]
Paviour 2007	GE	1.5	1000	3	NC	7	0.705 ± 0.023	63.1 ± 8.6				
					PD	12	0.714 ± 0.037	65.5 ± 9.2	NA	13.3 ± 6.7	2.8 ± 0.6	16.7 ± 5.1
					MSA-P	11	0.878 ± 0.15	62.0 ± 7.7	NA	5.4 ± 1.6	3.9 ± 0.8	26.8 ± 9.7
					PSP	19	0.71 ± 0.03	65.9 ± 6.2	NA	4.5 ± 1.8	3.5 ± 0.7	20.4 ± 7.9
Tsukamoto 2012	GE	3.0	1000	3	NC	18	0.737 ± 0.056	66.3 ± 9.9	8 (10)			
					PD	17	0.748 ± 0.054	71.1 ± 6.3	8 (9)	6.0 ± 3.0	NA	NA
					MSA-P	5	0.791 ± 0.045	NA	NA	NA	NA	NA
					PSP	20	0.748 ± 0.071	74.6 ± 5.7	14 (6)	4.0 ± 3.0	NA	NA
Wadia 2013	GE	1.5/3.0	1000	NA	NC	64	0.75 ± 0.13	57.3 ± 11.3	23 (41)			
					PD	57	0.69 ± 0.17	65.8 ± 10.6[b]	41 (20)[b]	7.0 ± 5.32[b]	2.6 ± 0.9[b]	NA
					MSA-P	15	0.80 ± 0.10	65.5 ± 12.4	8 (7)	3.9 ± 1.42	3.5 ± 1.0	NA
					PSP	21	0.71 ± 0.09	68 ± 8.4	17 (4)	4.6 ± 4.18	3.7 ± 0.9	NA

Abbreviations: ADC, apparent diffusion coefficient; HY, Hoehn-Yahr stage; MSA-P, multiple system atrophy with predominant parkinsonian features; NA, not available; NC, normal control; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SD, standard deviation; UPDRS, unified Parkinson's disease rating scale; yr, year.

[a] Median (range).

[b] These values were based on 61 patients with Parkinson's disease.