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Clinical Short Communication

Predictors of cognitive impairment in multiple system atrophy

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ABSTRACT

Objective: To determine predictors of cognitive impairment and frontal dysfunction in patients with multiple system atrophy (MSA).
Methods: We recruited 59 patients with MSA and determined the predictors of a decline in the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores.
Results: The MMSE scores negatively correlated with disease duration, Unified MSA Rating Scale (UMSARS) part 1 and 4 scores, and residual urine volume, and positively correlated with the coefficient of variation of electrocardiographic RR intervals. The FAB scores negatively correlated with the UMSARS part 2 score, periventricular hyperintensity grade, and deep white matter hyperintense signal grade. A significant predictor of rapidly progressive cognitive impairment was a high residual urine volume.
Conclusions: Impairment of global cognitive function correlates with the long-term disease duration, global disability due to the disease, and autonomic dysfunction, whereas frontal dysfunction correlates with motor function and degeneration of cerebral white matter.

1. Introduction

Based on a comprehensive evidence-based review, the Neuropsychology Task Force of the MDS Multiple System Atrophy (MODIMSA) Study Group suggests that cognitive impairment is present in patients with multiple system atrophy (MSA) more frequently than previously considered and that frontal dysfunction is the most common presentation among them [1]. Although the influence of disease duration on cognitive impairment is still unclear [2,3], patients with early cognitive impairment have been described [4], and in some patients, the cognitive impairment has preceded motor impairment [5]. However, little is known about the clinical features that predict the early or rapid development of cognitive dysfunction. Furthermore, although neuropathological studies have shown widespread subcortical degenerative changes in patients with MSA [6], the influence of white matter lesions on magnetic resonance imaging (MRI) scans on cognitive impairment has not been examined.

In the present study, we analyzed predictors of cognitive impairment and frontal dysfunction as well as rapidly progressive cognitive impairment in patients with MSA.

2. Methods

2.1. Patients

All procedures were performed after participants had provided written informed consent. Ethical approval for the present study was provided by the Institutional Ethics Committee of the Niigata University Medical and Dental Hospital. We performed a single-hospital study. A total of 66 consecutive patients with MSA admitted to our hospital between January 2007 and December 2015 were enrolled in the present study. All patients were diagnosed with probable MSA according to the diagnostic criteria delineated by Gilman et al. [7] Seven patients were excluded because their cognitive function was not sufficiently evaluated for their severe cognitive and motor impairment (In the two patients, meaningful communication was impossible due to severe dysarthria and writing disturbance. In the two patients, spontaneous speech and movement had decreased markedly. In the three patients, conversation was impossible due to tracheotomy). A total of 59 patients (28 men, 31 women) were included in the analysis.

2.2. Clinical assessments

For medical history, we defined the time when the symptom

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Table 1
Characteristics of the patients.

Age at admission (years)	64 ± 8.7
Sex (male:female)	28:31
Disease duration (months)	50 ± 31
Age at onset (years)	60 ± 9.0
Clinical subtypes (MSA-C:MSA-P)	46:13
MMSE	26 ± 3.2
FAB	14 ± 2.7
UMSARS part 1	22 ± 9.1
UMSARS part 2	23 ± 9.8
UMSARS part 4	3 (2–4)
Maximal decrease in SBP (mm Hg)	25 ± 17
Maximal decrease in DBP (mm Hg)	12 ± 11
CV_{RR} (%)	1.70 ± 0.88
Residual urine volume (ml)	184 ± 161
AHI	35.3 ± 28.1
ESS	6 ± 5
Premotor symptoms	14 (24%)
Erectile dysfunction	12 (43%)
Constipation	41 (69%)
Snore/stridor	36 (61%)
RBD	17 (29%)
PVH grade	1 (1–2)
DWMH grade	1 (0.75–2)

Data are expressed as means ± standard deviations for the continuous data, as medians (interquartile ranges) for the ordinal data, and as numbers and percentages or ratio for the nominal data. Abbreviations: MSA-C = cerebellar-predominant MSA; MSA-P = multiple system atrophy with predominant Parkinsonian features; MMSE = Mini-Mental State Examination, FAB = Frontal Assessment Battery; UMSARS = Unified Multiple System Atrophy Rating Scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; AHI = apnea hypopnea index; ESS = Epworth Sleepiness Scale; RBD = REM sleep behavior disorder; PVH = periventricular hyperintensity; DWMH = deep white matter hyperintense signals.

associated with MSA (whether motor or non-motor symptom) was first confirmed by patients or their families, as disease onset. If the onset was amibiguous from the history, we defined the time when there was no apparent symptom as onset. We assessed global cognitive function using the Mini-Mental State Examination (MMSE) and frontal lobe function using the Frontal Assessment Battery (FAB). We also assessed clinical severity using the Unified MSA Rating Scale (UMSARS) [8], autonomic dysfunction using the Schellong Test, the coefficient of variation of electrocardiographic RR intervals (CV_{RR}), residual urine volume using ultrasonography, and sleep disturbance using the Apnea-Hypopnea Index (AHI) on polysomnography and the Epworth Sleepiness Scale (ESS). We also assessed the presence of premotor symptoms, symptoms related to autonomic dysfunction (erectile dysfunction and constipation), and sleep disturbance (snore, stridor, and REM sleep behavior disorder (RBD)). In addition, we examined MRI findings within 6 months of the first admission. We evaluated the grades of periventricular hyperintensity (PVH) and deep white matter hyperintense signals (DWMH) on T2-weighted images (T2WI) as reported previously [9].

2.3. Data analysis

Data are expressed as means ± standard deviations for the continuous data, as medians (interquartile ranges) for the ordinal data, and as numbers and percentages for the nominal data. We analyzed predictors related to a decline in the MMSE and the FAB scores with a simple linear regression analysis for the continuous data and an ANOVA for the discrete data, followed by a Dunnett post hoc test. After finding a significant relationship between MMSE scores and disease duration, we categorized patients that were below the 68% prediction interval (equal to ± 1 standard deviation of the normal distribution) as belonging to a rapidly progressive cognitive impairment (RCI) group and the remaining patients to a non-RCI group to determine the factors related to the rapid progression of cognitive impairment. Then, we compared the RCI group and non-RCI group using simple and multiple logistic regression analyses. We used R version 3.1.2 environment (R core team 2014).

Table 2
Factors related to a decline in the Mini-Mental State Examination and Frontal Assessment Battery scores.

	MMSE		FAB	
	Regression coefficient	*p* value	Regression coefficient	p value
Age at admission	−0.06	0.23	−0.07	0.12
Male	−0.07	0.94	−0.62	0.40
MSA-P	−1.94	0.05	−0.83	0.35
Disease duration*	−0.03	0.03	−0.008	0.52
Age at onset	−0.02	0.69	−0.05	0.21
UMSARS part 1*	−0.11	0.02	−0.06	0.16
UMSARS part 2†	−0.09	0.06	−0.08	0.03
UMSARS part 4*	−0.91	0.006	−0.46	0.12
Maximal decrease in SBP	0.02	0.46	0.002	0.95
Maximal decrease in DBP	0.01	0.71	−0.04	0.29
CV_{RR}*	1.21	0.01	0.68	0.13
Residual urine volume*	−0.008	0.002	−0.003	0.27
AHI	0.0008	0.96	−0.03	0.06
ESS	−0.05	0.66	−0.08	0.34
Premotor symptoms	−0.28	0.78	−0.38	0.66
Erectile dysfunction (male only)	−1.44	0.32	−0.10	0.93
Constipation	0.83	0.37	0.36	0.66
Snore/stridor	0.73	0.40	−0.81	0.28
RBD	−0.75	0.42	−0.51	0.53
PVH grade†	−0.93	0.10	−1.22	0.01
DWMH grade†	−0.53	0.34	−1.18	0.01

Abbreviations: MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; MSA-P = multiple system atrophy with predominant Parkinsonian features; UMSARS = Unified Multiple System Atrophy Rating Scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; AHI = apnea hypopnea index; ESS = Epworth Sleepiness Scale; RBD = REM sleep behavior disorder; PVH = periventricular hyperintensity; DWMH = deep white matter hyperintense signals.
* $p < 0.05$ vs MMSE.
† $p < 0.05$ vs FAB.

3. Results

3.1. Patient characteristics

Mean age at onset and disease duration were 60 ± 9.0 years old (range, 42–80 years) and 50 ± 31 months (range, 11–160 months), respectively. Forty-six patients (78%) had predominant cerebellar features (MSA-C), and 13 patients (22%) had MSA-P. The number of MSA-P patients was small because there are fewer patients with MSA-P in the Japanese population [10]. Means or medians of MMSE, FAB, UMSARS part 1, part 2 and part 4 scores were 26 ± 3.2, 14 ± 2.7, 22 ± 9.1, 23 ± 9.8, and 3 (2–4), respectively. Means of CV_{RR} and residual urine volume were 1.70 ± 0.88% and 184 ± 161 ml, respectively. Medians of PVH grade and DWMH grade were 1 (1, 2) and 1 (0.75–2) (Table 1).

3.2. Factors related to declining MMSE and FAB scores

A simple linear regression analysis and ANOVA revealed that the MMSE scores negatively correlated with the disease duration ($p = 0.03$), UMSARS part 1 score ($p = 0.02$), UMSARS part 4 score ($p = 0.006$), and residual urine volume ($p = 0.002$), but positively correlated with CV_{RR} ($p = 0.01$) (Table 2). Post hoc test revealed a significant difference between UMSARS part 4 scores = 2 and ≥ 4 (Fig. 1A). The FAB scores were correlated with the UMSARS part 2 scores ($p = 0.03$), PVH grade ($p = 0.01$), and DWMH grade (p = 0.01). Post hoc test revealed a significant difference between a PVH grade of 0