Clinical Parkinsonism & Related Disorders 3 (2020) 100037

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Heightened risk of early vocal fold motion impairment onset and dysphagia in the parkinsonian variant of multiple system atrophy: a comparative study ☆,☆☆

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ARTICLE INFO

Article history:
Received 13 July 2019
Received in revised form 7 November 2019
Accepted 25 November 2019
Available online 16 January 2020

Keywords:
Multiple system atrophy
Parkinsonian variant type
Vocal fold motion impairment
Sleep apnea
Dysphagia

ABSTRACT

Objective: We compared differences in frequency and timing of onset of the following clinical events between the cerebellar and parkinsonian variants of multiple system atrophy (MSA-C and MSA-P, respectively): type of operation including tracheostomy and/or aspiration prevention surgery, vocal fold motion impairment (VFMI), sleep apnea (SA), introduction of mechanical ventilation (MV), and dysphagia. The risks of these events cooccurring with either MSA-C or MSA-P were compared.

Methods: We retrospectively assessed clinical outcomes only of patients with MSA who presented at the Department of Otolaryngology of the University of Tokyo Hospital between 2008 and 2018. The proportion and timing of onset events between MSA-C and MSA-P and risks of onset were compared using chi-square tests and Cox proportional hazard models adjusted for age, sex, and disease severity, respectively.

Results: We identified 113 patients (median age: 60 years, 72 men [64%]). The frequency and timing of VFMI, SA, MV, dysphagia, and surgeries were 55 patients (49%) and 76 (95% CI 61–91) months after MSA onset, 85 (75%) and 41 (32–50), 36 (32%) and 100 (73–127), 77 (68%) and 43 (36–50), and 25 (22%) and 102 (84–120), respectively. Twenty-seven patients (24%) had MSA-P and higher risk of VFMI ($p < .001$), SA ($p = .030$), and dysphagia ($p = .017$) than did patients with MSA-C.

Conclusion: While MSA-P is less common, it may involve heightened risk of VFMI and dysphagia early onset. Thus, careful follow-up for VFMI, SA, and dysphagia may be needed for these patients.

Criteria for Rating Diagnostic Accuracy Studies: Class II.

1. Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder with autonomic dysfunction, parkinsonian disorder, and cerebellar dysfunction as the main symptoms. MSA is classified into the parkinsonian (MSA-P) and cerebellar (MSA-C) variant types [1].

In patients with MSA, respiratory disorder frequently occurs during sleep, sometimes resulting in sleep apnea (SA). Causes of SA include upper airway obstruction and/or central sleep disturbance [2], and the frequency of obstructive SA ranges from 15% to 37% [3]. Inspiratory stridor, a high-pitched sound experienced by 34% of patients with MSA [3], is another characteristic respiratory symptom induced by upper airway obstruction that is often comorbid with SA [4,5], developing at a mean of 5.8 years after the onset of MSA [2]. Laryngeal stridor was reportedly the initial symptom in 4% of individuals with MSA [2]. Upper airway obstruction in patients with MSA can induce sudden death, and the causes of upper airway obstruction include vocal fold motion impairment (VFMI) and floppy epiglottis. Thus, based on the grade of upper airway stenosis, tracheostomy may be required [6].

Dysphagia is a subjective complaint that presents in 73% of patients with MSA [7]; it is one of the most important factors for determining the timing of tracheostomy because MSA is progressive. Aspiration prevention surgery with simultaneous tracheostomy is gradually replacing simple tracheostomy in the treatment of patients with progressing dysphagia, and aspiration prevention surgery is considered to retain oral intake and to improve the quality of life of patients [8].

☆ Study fundingThis work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C) [grant number 16K20231].

☆☆ Conflict of interest statement

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http://dx.doi.org/10.1016/j.prdoa.2020.100037

A comparison of MSA-P and MSA-C revealed that the clinical courses of autonomic dysfunction and movement impairment are similar between the two conditions [9]; however, there have been some reports of differences in the survival rates of patients with MSA-P and MSA-C [9–11] and of differences in the frequency or timing of clinical events between the two conditions, which might explain their divergent outcomes, whose causes presently remain unknown. The present study aimed to elucidate the frequency and timing of onset of symptoms such as VFMI, SA, introduction of mechanical ventilation (MV), dysphagia, and respiratory-related surgeries (tracheostomy and aspiration prevention surgery) in MSA-P and MSA-C and compare the risks of their onsets between the two conditions.

2. Method

2.1. Ethics

This study was approved by the Human Ethics Committee of the University of Tokyo (No. 2487). Written informed consent was obtained from every patient and patient anonymity was preserved.

2.2. Study design and patients

This was a retrospective cohort study. This study enrolled patients from those who were previously diagnosed with MSA before presenting at the Department of Otolaryngology of the University of Tokyo Hospital from 2008 to 2018. We retrospectively collected clinical data by reviewing the electronic medical records for each enrolled patient and assessed the frequency and timing of the onset of symptoms such as VFMI, SA, introduction of MV, and dysphagia, as well as those of surgeries. We limited the analysis to these four events in this study, as otolaryngologists mainly evaluate the upper airway-related findings including swallowing function and vocal fold movement. All patients with MSA who presented at our department were included in this study, and exclusion criteria were not set.

Onset of MSA was defined as the initial presentation of any motor or autonomic symptom. The observation periods of the patients that underwent operation spanned from the onset of MSA to the performance of the operation, while that of those who did not receive operation spanned from the onset of MSA to the last consultation day at the Department of Otolaryngology. We set the baseline as the timing of MSA diagnosis. MSA severity was evaluated at baseline and designated from Stages 1 to 5. Stage 1 was defined as the ability to walk without support; Stage 2 was defined as aid-required walking (use of a walking aid or a companion's arm for support) but not at all times; Stage 3 was defined as aid-required walking at all times; Stage 4 was defined as a wheelchair-bound state (wheelchair use at all times); Stage 5 was defined as a bedridden state (complete loss of the ability for independent activity) [12]. VFMI was diagnosed using a laryngeal fiberscope. SA was indicated by an Apnea Hypopnea Index (AHI) of >5. Onset of SA was defined as the time at which diagnosis was made via polysomnography or the commencement of obvious snoring episodes. Introduction of MV indicates the introduction of continuous positive airway pressure for SA or MV via tracheostomy. Onset of dysphagia was defined as the time at which obvious symptoms, such as choking or difficulty in swallowing, developed or dysphagia was diagnosed by swallowing videofluorography and/or swallowing videoendoscopy. Operations included tracheostomy and/or aspiration prevention surgery. For the cases in which both operations were performed, the date of operation was defined as the date of the earliest operation.

2.3. Statistical analysis

We analyzed the data with Bell Curve for Excel (version 2.21, Social Survey Research Information Co., Ltd., Tokyo, Japan). To compare baseline measures, such as age, sex, and observation period, we used the Mann–Whitney test for continuous variables and chi-squared (χ^2) tests or Fisher's exact test for categorical variables. We used a Kaplan–Meier analysis to assess the time from the onset of MSA to the onset of each clinical event. For comparison among subtypes, we used the log-rank test. The parameters showing significant differences in the log-rank test were used in a Cox regression model adjusted for age, sex, and disease severity to calculate the hazard ratio of MSA-P to MSA-C. A p value $<.05$ was considered to be significant.

3. Results

3.1. Patient characteristics

We identified 113 eligible patients; the median age at onset of MSA was 60 (interquartile range [IQR], 53–66) years; 72 (64%) of the patients were men; the median observation period was 47 (IQR, 28–76) months; the duration from MSA onset to baseline was 29 (IQR, 20–39) months. These characteristics were not significantly different between the patients with MSA-C and those with MSA-P (Table 1).

3.2. Frequency of respiratory-related clinical events

VFMI was observed in 55 patients (49%), SA in 85 patients (75%), MV in 36 patients (32%), dysphagia in 77 patients (68%), and surgeries were performed in 25 patients (22%) (Table 2). VFMI occurred in 74% of patients with MSA-P, while only in 40.7% of those with MSA-C ($p = .003$). In addition, although not statistically significant, there was also a clear difference, approaching significance, for SA ($p = .06$) and dysphagia ($p = .09$) (Table 2).

3.3. Onsets of respiratory-related clinical events

The median time from MSA onset to those of VFMI, SA, MV, and dysphagia (by Kaplan–Meier analysis) was 76 months (95% CI 61–91), 41 months (95% CI 32–50), 100 months (95% CI 73–127), and 43 months (95% CI 6–50), respectively; that from MSA onset to surgery was 102 months (95% CI 84–102). Fig. 1 shows the relative accumulation of respiratory events between the two groups. Between MSA-P and MSA-C, median duration from MSA onset to those of VFMI (42 months [95%

Table 1
Characteristics of the patients with multiple system atrophy.

Characteristic		All	MSA-P	MSA-C	p value
Patients-no.(%)		113	27 (23.9)	86 (76.1)	
Age-years median [IQR]		60 [53–66]	60 [53–68]	59 [53–65]	0.58
Male-no.(%)		72 (63.7)	14 (51.9)	58 (67.4)	0.15
Observation period-mth. Median [IQR]		47 [28–76]	39 [29–58]	51 [27–78]	0.26
Duration from onset to baseline -mth. Median [IQR]		29 [20–39]	31 [28–41]	29 [19–38]	0.26
Severity stage at baseline-no. (%)	1	36 (31.9)	10 (27.8)	26 (72.2)	
	2	50 (44.2)	10 (20.0)	40 (80.0)	
	3	21 (18.6)	6 (28.6)	15 (71.4)	
	4	6 (5.3)	1 (16.7)	5 (83.3)	
	5	0 (0)	0 (0)	0 (0)	

MSA-C: the cerebellar variant type of multiple system atrophy, MSA-P: the parkinsonian variant type of multiple system atrophy, no: number, IQR: interquartile range, mth: month.

Table 2
Frequency of clinical events.

Clinical events	All (n = 113)	MSA-P (n = 27)	MSA-C (n = 86)	p value
Vocal cord motion impairment- no.(%)	55 (48.7)	20 (74.1)	35 (40.7)	0.003**
Sleep apnea- no.(%)	85 (75.2)	24 (88.9)	61 (70.9)	0.06
Introduction of mechanical ventilation- no.(%)	36 (31.9)	8 (29.6)	28 (32.6)	0.82
Dysphagia- no.(%)	77 (68.1)	22 (81.5)	55 (64.0)	0.09
Surgery- no.(%)	25 (22.1)	6 (22.2)	19 (22.1)	0.99

MSA-P: the parkinsonian variant type of multiple system atrophy, MSA-C: the cerebellar variant type of multiple system atrophy, no: number. **: $P < .01$.

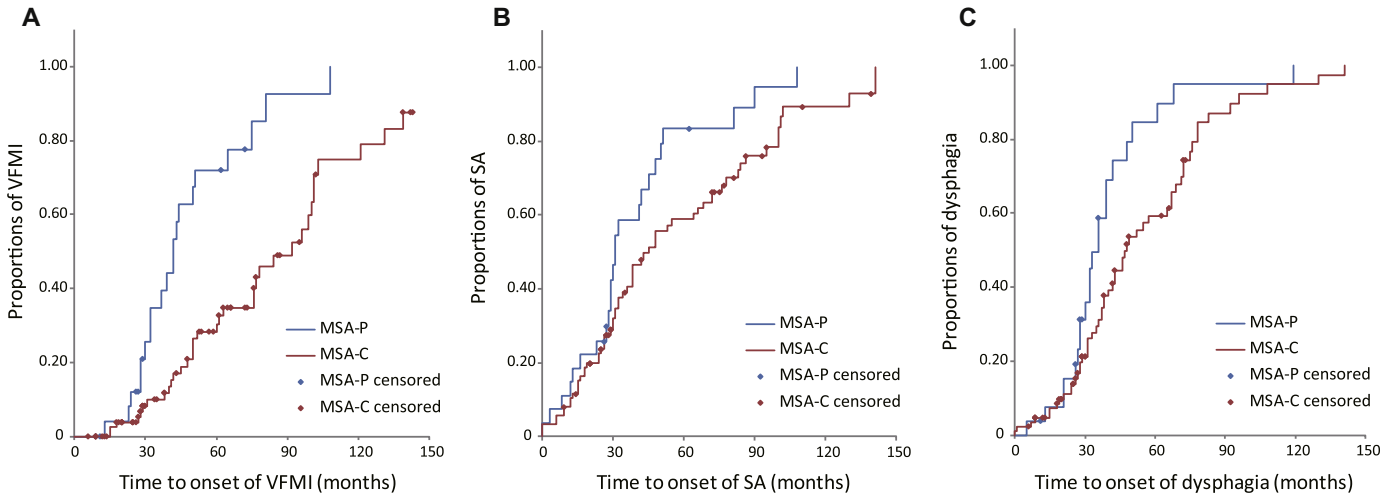

Fig. 1. Cumulative clinical events of VFMI, SA, and dysphagia according to subtype. A: Cumulative clinical events of VFMI. B: Cumulative clinical events of SA. C: Cumulative clinical events of SA. MSA-C: the cerebellar variant type of multiple system atrophy, MSA-P: the parkinsonian variant type of multiple system atrophy. VFMI: vocal fold motion impairment. SA: sleep apnea.

CI 36–48] vs 92 months [95% CI 69–115], $p < .001$, Fig. 1-A), SA (31 months [95% CI 27–35] vs 45 months [95% CI 36–54], $p = .033$, Fig. 1-B) and dysphagia (36 months [95% CI 30–42] vs 48 months [95% CI 38–58], $p = .015$, Fig. 1-C) were significantly shorter in patients with MSA-P (Table 3). In addition, the Cox regression model adjusted for age, sex, and disease severity revealed that MSA-P was associated with higher risks of onset of VFMI (hazard ratio [HR] 3.44, 95% CI 1.91–6.20, $p < .001$), SA (HR 1.70, 95% CI 1.05–2.76, $p = .031$), and dysphagia (HR, 1.85, 95% CI 1.12–3.07, $p = .017$) (Table 3).

4. Discussion

The present study investigated the frequencies of respiratory-related clinical events, such as VFMI, SA, MV, dysphagia, as well as that of surgeries among patients with MSA-C or MSA-P by conducting a retrospective medical chart review; it is thereby, to the best of our knowledge, the first to compare the risks of comorbidities between respiratory-related clinical events and MSA-C or MSA-P. MSA-P was associated with higher risks of developing VFMI, SA, and dysphagia. The frequency of developing VFMI was higher among patients with MSA-P, and VFMI, SA, and dysphagia occurred earlier in patients with MSA-P than in those with MSA-C.

MSA-P and MSA-C induce many of the same symptoms and are evinced by similar scores on neurologic and motor evaluations, as well as on assessments of functional status in daily living [9]. Though MSA-P has been associated with shorter survival than has MSA-C [10], other reports have found that the survival rates do not differ between the two conditions [9,11]. To date, differences in most clinical events between MSA-P and MSA-C remain incompletely understood.

Respiratory stridor, sleep apnea, and respiratory insufficiency are part of the clinical spectrum of MSA [13,14]. Respiratory stridor can be caused by floppy epiglottis, floppy arytenoid, and VFMI [6,15,16]. There are two plausible hypotheses for VFMI-related stridor [2]: (1) a severe loss of neurons in the nucleus ambiguous results in the hypoactivity of the laryngeal abductor and neurogenic atrophy in the posterior cricoarytenoid muscle and (2) dystonia induced by hyperactivity of the laryngeal adductor muscles.

VFMI can be observed in patients with Parkinson's disease (PD), some of whom have laryngeal dystonia presenting as irregular, uncontrolled vocal spasms [17]; such spontaneous activity of intrinsic laryngeal muscles during vocal rest has been revealed by laryngeal electromyography [2,18]. In

Table 3
Median duration from onset of MSA to that of clinical events.

Clinical events	All (n = 113)	MSA-P (n = 27)	MSA-C (n = 86)	p value[a]	Hazard Ratio[b]	Adjusted p[b]
Vocal fold motion impairment - mth. [95% CI]	76 [61–91]	42 [36–50]	92 [69–115]	<0.001**	3.44 [1.91–6.20]	< 0.001**
Sleep apnea - mth. [95% CI]	41 [32–50]	31 [27–35]	45 [36–54]	0.033*	1.70 [1.05–2.76]	0.031*
Introduction of mechanical ventilation - mth. [95% CI]	100 [73–127]	97 [50–144]	101 [75–127]	0.541		
Dysphagia - mth. [95% CI]	43 [36–50]	36 [30–42]	48 [38–70]	0.015*	1.85 [1.12–3.07]	0.017*
Surgeries - mth. [95% CI]	102 [84–120]	81 [57–105]	102 [57–147]	0.173		

MSA-P: the parkinsonian variant type of multiple system atrophy, MSA-C: the cerebellar variant type of multiple system atrophy, a: Log-rank test, b: Cox proportional hazard model adjusted for age, sex, and severity stages, mth: month, 95% CI: 95% confidence interval.

this study, we revealed that patients with MSA-P developed VFMI in higher frequency and sooner after MSA onset than did their MSA-C counterparts. However, further study is required to elucidate the relationship between systematic symptoms and VFMI.

SA can be divided into two types: obstructive and central SA caused by upper-airway obstruction and degeneration of the sleep centers in the brain [1,4]. Obstructive SA is more frequent than is central SA, occurring in up to 40% of patients with MSA [19]. Sudden death is not uncommon in patients with MSA and usually occurs during sleep [2,20], but it is unclear whether the sudden death results from VFMI and/or central hypoventilation or from SA or other causes. Considering that obstructive SA can be partly caused by laryngeal constriction, including VFMI, based on our findings, vocal fold movement should be inspected, especially in patients with MSA-P.

Dysphagia is one of the most frequent complications of MSA and dramatically affects quality of life [8,12,21,22]. In tandem with impaired airway protection and esophageal sphincter contraction disturbances, delayed oral and pharyngeal phases of swallowing may cause acute aspiration and pneumonia [23,24]. Patients with MSA-P have higher risk of earlier beginning of diet modification [25], and this might support our result that patients with MSA-P developed dysphagia earlier than those with MSA-C. In previous studies, we have reported impaired relaxation of the upper esophageal sphincter (UES), abnormal UES pressure, and a pattern of uncoordinated proximal esophageal contraction pressure during swallowing and resting, regardless of MSA phenotype [24,26]. Preganglionic cholinergic dysfunction and, specifically, the loss of the dorsal vagal nucleus innervating the digestive system reportedly account for oropharyngeal and esophageal swallowing impairments in patients with MSA [24,27]. It has been reported that the mechanisms underlying dysphagia in patients with MSA and PD can partially overlap [28,29]. The results of this study also support the possible impact of parkinsonism on swallowing in patients with MSA-P. It is possible that the narrowing of the upper airway worsens with dysphagia. Considering that dysphagia is closely related to VFMI, early detection of dysphagia in patients with MSA is essential, especially in those with MSA-P. For patients with severe VFMI and moderate-to-severe dysphagia, aspiration prevention surgery should be considered as a means to improve their oral intake and their quality of life [8].

This study is subject to several limitations. First, as a single-center retrospective chart review, the sample size was small and the included patients were limited; this study included all patients who were diagnosed with MSA at the Department of Neurology of the University of Tokyo Hospital and those who were referred to the Department of Otolaryngology for operations or evaluation, and, thus, the observed prevalence of each clinical event is likely to have been overestimated and may not be generalizable to all patients with MSA. Second, the sample size of the patients with MSA-P was small because MSA-P is infrequent in Japan in contrast to Western countries [12]. Third, we did not include data on stridor, as the records were incomplete. It is difficult to distinguish between stridor and snoring by reviewing the electronic medical records, although stridor is one of the most important respiratory symptoms. Our results may be difficult to generalize, and these drawbacks indicate the need for further research to validate our findings.

5. Conclusion

We revealed that patients with MSA-P more frequently develop VFMI and are at greater risk of early onset of VFMI, SA, and dysphagia relative to patients with MSA-C. Physicians should consider vocal fold movement, swallowing function, and SA in patients with MSA, especially in those with MSA-P, because these clinical events may progress more rapidly than in patients with MSA-C.

Disclosures

Declaration of Competing Interests

None.

Acknowledgement

This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C) [grant number 16 K20231].

Author contributions

R.U. developed the concept, designed the study, and collected and analyzed the data. K.T. and S.S. designed the study and collected and analyzed the data. T.G., T.S., and T.N. developed the concept and collected the data. T.Y contributed to the interpretation of the results and the supervision of this project. All authors contributed to the interpretation of the data and the writing of the manuscript.

Patient consent

Written informed consent was obtained from every patient, and patient anonymity was preserved.

Ethical approval

This study was approved by the Human Ethics Committee of the University of Tokyo (No. 2487).

Data sharing statement

All data related this study are available from the corresponding author upon reasonable request.

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