Journal of the Neurological Sciences 400 (2019) 25–29

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

The severity of motor dysfunctions and urinary dysfunction is not correlated in multiple system atrophy

Tatsuya Yamamoto[a,*], Yoshitaka Yamanaka[a], Atsuhiko Sugiyama[a], Shigeki Hirano[a], Tomoyuki Uchiyama[a,c], Masato Asahina[d], Ryuji Sakakibara[b], Satoshi Kuwabara[a]

[a] Department of Neurology, Chiba University Graduate School of Medicine, Chiba, Japan
[b] Neurology Division, Department of Internal Medicine, Sakura Medical Center, Toho University, Sakura, Japan
[c] Department of Neurology, International University of Health and Welfare, Ichikawa, Japan
[d] Neurology Clinic Tsudanuma, Chiba, Japan

A B S T R A C T

Objective: Although it is well known that patients with multiple system atrophy (MSA) cerebellar dominant type (MSA-C) show severe autonomic dysfunction, the relationship between autonomic and motor dysfunction remains uncertain. Previously we reported that severe urinary voiding dysfunction is useful in differential diagnosis of MSA and other diseases. Herein, we aimed to clarify the relationship between the severity of motor dysfunctions and urinary dysfunction.

Method: This study is a retrospective review of 46 patients with MSA-C diagnosed according to Gilman's second consensus criteria. The severity of motor dysfunctions was evaluated using International Cooperative Ataxia Rating Scale (ICARS). Urinary voiding dysfunction was evaluated by measuring post-void residual (PVR). The mean duration of motor unit potentials in external anal sphincter muscles on electromyography, which represents the severity of neurodegeneration in Onuf's nucleus, was also examined.

Results: The mean age of patients was 63.8 ± 8.2 years and mean disease duration was 3.0 ± 1.9 years. The mean ICARS score was 40.1 ± 14.7. The mean PVR was 119.1 ± 102 ml and the mean duration of motor unit potentials (MUPs) in anal sphincter electromyography was 9.2 ± 2.2 ms. The correlation coefficient between ICARS and PVR was 0.093 ($p = .539$), and between ICARS and mean duration of MUPs was 0.105 ($p = .811$). A significant positive correlation ($r = 0.296$, $p = .005$) was noted between PVR and the mean duration of MUP.

Conclusion: Motor and urinary dysfunctions were not correlated in MSA-C.

1. Background

Multiple system atrophy (MSA) is clinically characterized by the combination of autonomic, cerebellar and extrapyramidal dysfunction. Autonomic dysfunction is required for the diagnosis of MSA and clinically classified into MSA-C (cerebellar dominant) and MSA-P (parkinsonism dominant) depending on motor phenotype [1]. The prevalence of MSA-C is higher than MSA-P in Japan [2,3].

It is generally challenging to differentiate MSA-C from other forms of spino-cerebellar degeneration (SCD) and MSA-P from Parkinson's disease (PD) [1]. Autonomic dysfunction is often not clearly evident in some patients with MSA. We have previously reported that cerebellar ataxia was one of the initial symptoms in 79% of patients with MSA-C, while it was the initial symptom of Parkinsonism in 68% of patients with MSA-P [4]. Because clinical manifestations of MSA-C without apparent autonomic dysfunction usually mimics other forms of SCD and clinical manifestations of MSA-P without apparent autonomic dysfunction mimics PD, MSA may be sometimes misdiagnosed as pure cerebellar SCD or PD. [5] However, because the presence of autonomic dysfunction is required for the diagnosis of MSA, MSA cannot be confirmed until the autonomic dysfunction emerges [6]. While the progression of motor and autonomic dysfunction may not be parallel in some patients with MSA, we do not know the precise relationship between these dysfunctions.

We have previously reported that urinary dysfunction was the most common initial symptom in MSA-C and MSA-P, followed by orthostatic hypotension and erectile dysfunction among autonomic symptoms [7]. Several reports have suggested that urinary dysfunction precedes orthostatic hypotension in the majority of patients with MSA. Since MSA-C is more prevalent than MSA-P in Japan and urinary dysfunction is prevalent and severe [2,3], we aimed to clarify the relationship between the severity of motor dysfunctions and urinary dysfunction evaluated by urodynamic study (UDS).

* Corresponding author at: Department of Neurology, Chiba University Graduate School of Medicine, 1-8-1 Inohana Chuo-ku, Chiba 260-8670, Japan.
E-mail address: tatsuya-yamamoto@mbc.nifty.com (T. Yamamoto).

https://doi.org/10.1016/j.jns.2019.03.005
Received 22 January 2019; Received in revised form 24 February 2019; Accepted 9 March 2019
Available online 12 March 2019
0022-510X/

2. Materials and methods

We retrospectively reviewed the medical records of 46 patients with MSA-C who were diagnosed with probable or possible MSA, according to Gilman's second consensus criteria, from January 2007 to April 2014 in Chiba University Hospital. All patients were interviewed and carefully examined by neurologists who were experienced in the movement disorder field. Family members were also interviewed to accurately evaluate the patients' natural histories. Symptom onset was defined as the initial presentation of motor symptoms, including cerebellar and parkinsonian symptoms, or autonomic symptoms, including orthostatic hypotension or pelvic organ symptoms. The location of the initial motor symptoms (upper or lower limb) was also identified. The severity of motor dysfunctions was evaluated by the total score of International Cooperative Ataxia Rating Scale (ICARS).Urinary symptoms were evaluated using our original questionnaire [7,10]. All patients underwent brain magnetic resonance imaging (MRI).

3. Urodynamic study

A UDS was conducted by neurologists and a urologist who were familiar with free flowmetry and UDS findings. The neurologists carefully examined urinary dysfunction associated with neurological dysfunction. Maximum and average flow rates were obtained by performing free flowmetry before conducting the pressure flow study. After the voided volume was measured, post-void residual (PVR) was measured using transurethral catheterization. Normal volume was < 50 ml. Electromyographic cystometry was performed using a urodynamic computer (Janus; Life-Tec Inc., Houston, TX, USA) and an electromyography (EMG) computer (Neuropack Sigma; Nihon Kohden Inc., Tokyo, Japan). During the measurements, EMG of the anal sphincter was continuously recorded by inserting a coaxial needle electrode into the external anal sphincter (EAS) muscles. An 8F double-lumen catheter was passed through the urethra, and water (saline) cystometry was performed at an infusion rate of 50 ml/min while the patient was seated. Simultaneously, rectal pressure was measured using a balloon catheter and electronically subtracted from the intravesical pressure. Water cystometry was followed by a pressure flow study. Both free flowmetry and a pressure flow study were performed in the sitting position in the same environment. Each flow study tracing was reviewed by the neurologists and urologist. Falsely high Qmax values caused by abdominal straining were excluded.

Abnormal urodynamic findings during the storage phase included detrusor overactivity, defined as involuntary detrusor contractions during the filling phase. Quantitative parameters measured during the storage phase included bladder volume at the first desire to void (FDV) and at strong desire to void (SDV). An FDV of < 100 ml and an SDV of < 300 ml were considered abnormal. Maximum cystometric capacity was the volume at which the patient could no longer delay micturition. Abnormal urodynamic findings during the voiding phase included impaired bladder contractility. The degree of detrusor contraction was evaluated using Schäfer's nomogram. Impaired detrusor contractility included “weak” and “very weak” contractility in Schäfer's nomogram. The methods, definitions, and units employed conformed to the standards recommended by the International Continence Society [9].

4. External anal sphincter EMG

A disposable concentric needle electrode (needle diameter, 0.46 mm; Alpine Biomed, Skovlunde, Denmark) was inserted into the most superficial layer of the anal sphincter under audio guidance. A needle was inserted into the right (5 o'clock position) and the left (7 o'clock position) sphincter muscles, and a motor unit potential (MUP) analysis was performed. Five MUPs were recorded on each side. The position of the needle electrode was adjusted until continuous firing activities of 3–5 MUPs were visually observed. The rise time of the MUP was 300–500 μs. The location from which MUP was recorded was about 1 cm from the anal orifice to a depth of 3–6 mm. A gain of 100 μV at 5 ms/div was used. The amplifier filter was set at 5–10 kHz.

The MUPs were stored in the input buffer of the computer when the amplitude reached the threshold determined by the examiner. After visual confirmation that the 3–5 MUPs were continuously firing, the examiner manually set the threshold by moving the cursor for detecting the visually confirmed 3–5 MUPs. Subsequently, 64 MUPs were stored in the input buffer of the computer. The stored MUPs were classified into the four most similar MUPs using the auto MUP analysis software that was part of the EMG computer using the following procedure: the stored MUPs were numbered MUP1 through MUP64. The auto MUP analysis software recorded MUP1 as a template wave and calculated the correlation coefficient between MUP1 and MUP2. If the correlation coefficient exceeded 0.94, the software regarded MUP2 as identical to MUP1. Otherwise, MUP2 was regarded as a different wave from MUP1. The software repeated this procedure for the remaining MUPs and finally identified the four most similar MUPs. Onset of the MUP was automatically determined when both the slope and the voltage exceeded predefined thresholds (onset slope, 5 μV/ms; onset level, 20 μV) above or below the baseline voltage in this study. Termination of the MUP was determined by the same procedure. These values were used for automatically calculating the duration. Because this program could not identify late components (separate satellite potentials), the examiner checked the wave form and manually set the cursor to include late components. Late components were included in the total MUP duration. We repeated the above procedures for obtaining 10 different MUPs by moving the position of the electrode. The EMG computer calculated the mean duration, number of phases and amplitude of the 10 different MUPs obtained.

Neurogenic change was diagnosed when the mean duration of the MUPs was > 10 ms, including the late components. The method for performing External anal sphincter EMG (EAS-EMG) and the diagnostic criteria of neurogenic change in EAS-EMG were concurrent with those used in a previous study [10]. All EMG recordings were performed at Chiba University, and all results were examined using the same criteria. Since all authors had experience working at Chiba University, the duration criteria were well understood.

4.1. Statistical analysis

All data are expressed as mean ± standard error of mean, and all statistical analyses were performed using SPSS Version 22.0 (IBM, Armonk, USA). Spearman's correlation coefficient was used for calculating the relationship between ICARS scores and quantitative urodynamic parameters such as maximum cystometric capacity, PVR and mean duration of MUP, and qualitative parameters such as the presence of DO and bladder contractility evaluated by Schäfer's nomogram. Multivariate stepwise regression analysis was performed for determining which urodyamic parameters contribute to the ICARS score.

This study has been approved by the Chiba University Hospital Institutional Review committee. Approval from an ethical standards committee to conduct this study has also been received.

5. Results

Mean age of the 46 patients with MSA-C was 63.8 ± 8.2 years with a mean disease duration of 3.0 ± 1.9 years. The mean total ICARS score was 40.1 ± 14.7.

5.1. Urinary symptoms

The results of the urinary symptom questionnaire revealed that both storage symptoms (daytime and night time urinary frequency and urinary urgency) and voiding symptoms (delay, prolongation, intermittency and straining at urination) are prevalent in patients with MSA-

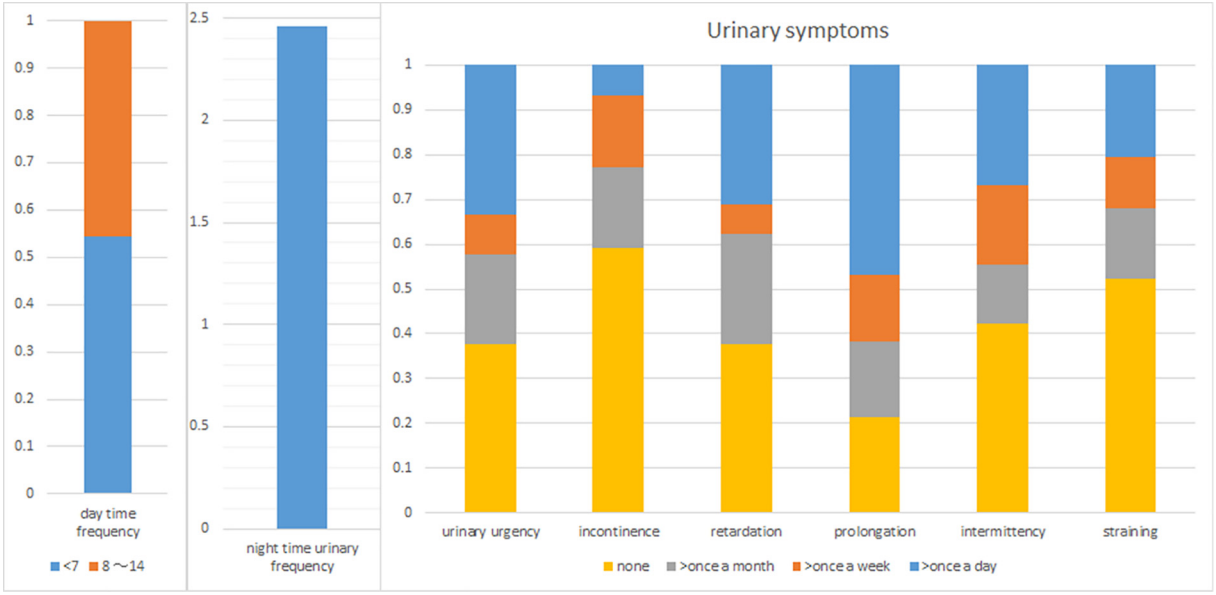

Fig. 1. Urinary symptoms.
The results of the urinary symptom questionnaire revealed that both storage symptoms (daytime and night time urinary frequency and urinary urgency) and voiding symptoms (delay, prolongation, intermittency and straining at urination) are prevalent in patients with MSA-C. The prevalence of incontinence was relatively low compared with other urinary symptoms (Fig. 1).

C. The prevalence of incontinence was relatively low compared with other urinary symptoms (Fig. 1).

5.2. Urodynamic study

The results of the UDS showed a high prevalence of detrusor overactivity (65.9%), decreased urinary flow rate, and large PVRs. The prevalence of detrusor-sphincter dyssynergia was low (19.64%). Mean PVR was 119.1 ± 102 ml and the mean duration of MUPs in the anal sphincter was 9.2 ± 2.2 ms. Results of the urodynamic parameters are listed in Table 1.

5.3. The correlational coefficients between the disease duration and ICARS, PVR, and mean duration of MUPs

The correlational coefficients between the disease duration and a total scores of ICARS, PVR, and mean duration of MUPs in anal sphincter electromyography was 0.131 ($p = .390$), −0.178 ($p = .111$), and − 0.059 ($p = .599$), respectively.

5.4. The correlational coefficients between urodynamic parameters and ICARS

The correlation coefficient between a total score of ICARS and PVR was 0.093 ($p = .539$) (Fig. 2a), and between a total score of ICARS and mean duration of MUPs in anal sphincter electromyography was 0.105 ($p = .811$) (Fig. 2b). None of the urodynamic parameters had significant correlations with the ICARS scores. The correlational coefficient between PVR and mean duration of MUP, 0.296, was significant ($p = .005$) (Fig. 2c).

Table 1
The results of urodynamic study.

Average flow rate (ml/s)	3.74 ± 0.33
Maximum flow rate (ml/s)	7.80 ± 0.67
First desired volume (ml)	173.46 ± 9.98
Maximum desired volume (ml)	341.84 ± 13.65
Post-void residual (ml)	119.10 ± 10.93
Prevalence of detrusor overactivity	65.90%
Prevalence of detrusor-sphincter dyssynergia	19.64%

5.5. Multivaritate stepwise regression analysis

None of the urodynamic parameters determine the scores of ICARS

6. Discussion

The present study revealed that none of the urodynamic parameters were significantly correlated with a total ICARS scores, indicating that the severity of motor dysfunctions and urinary dysfunction are not correlated in MSA-C. This suggests that the severity of motor dysfunctions and urinary dysfunction are not parallel, which may contribute to the misdiagnosis of MSA-C. We do not know the exact reasons why the severity of motor dysfunctions and urinary dysfunctions were not correlated. However, the present study also revealed that the disease duration did not significantly correlate with ICARS, PVR, and mean duration of MUPs, which suggested that the progression of motor dysfunctions and urinary dysfunctions were heterogeneous in MSA-C. Some MSA-C patients might show rapid progression of motor dysfunctions with mild deterioration of urinary dysfunction and vice versa. The heterogeneous progression of motor dysfunctions and urinary dysfunction might lead to the present result that a total ICARS score and urinary dysfunctions (PVR and mean duration of MUPs) were not correlated. In addition, we have previously reported that mean intervals between onsets of urinary symptoms and initial motor symptoms were 2.2 ± 0.25 years, which might influence the results of the relationship between the severity of motor dysfunction and urinary dysfunction [4]. Since the presence of autonomic dysfunction is necessary for the diagnosis of MSA, it is difficult to diagnose MSA with mild autonomic dysfunction even if there is rapid progression of motor dysfunctions with pontine and cerebellar atrophy on MRI. The results of the urinary symptoms questionnaire and the UDS showed that patients with MSA-C have both storage and voiding dysfunction comparable to that in previous studies [8,9].

The prevalence of urinary incontinence, which is required for probable MSA, was low compared with other urinary symptoms, suggesting that it may be difficult to make a diagnosis of probable MSA.

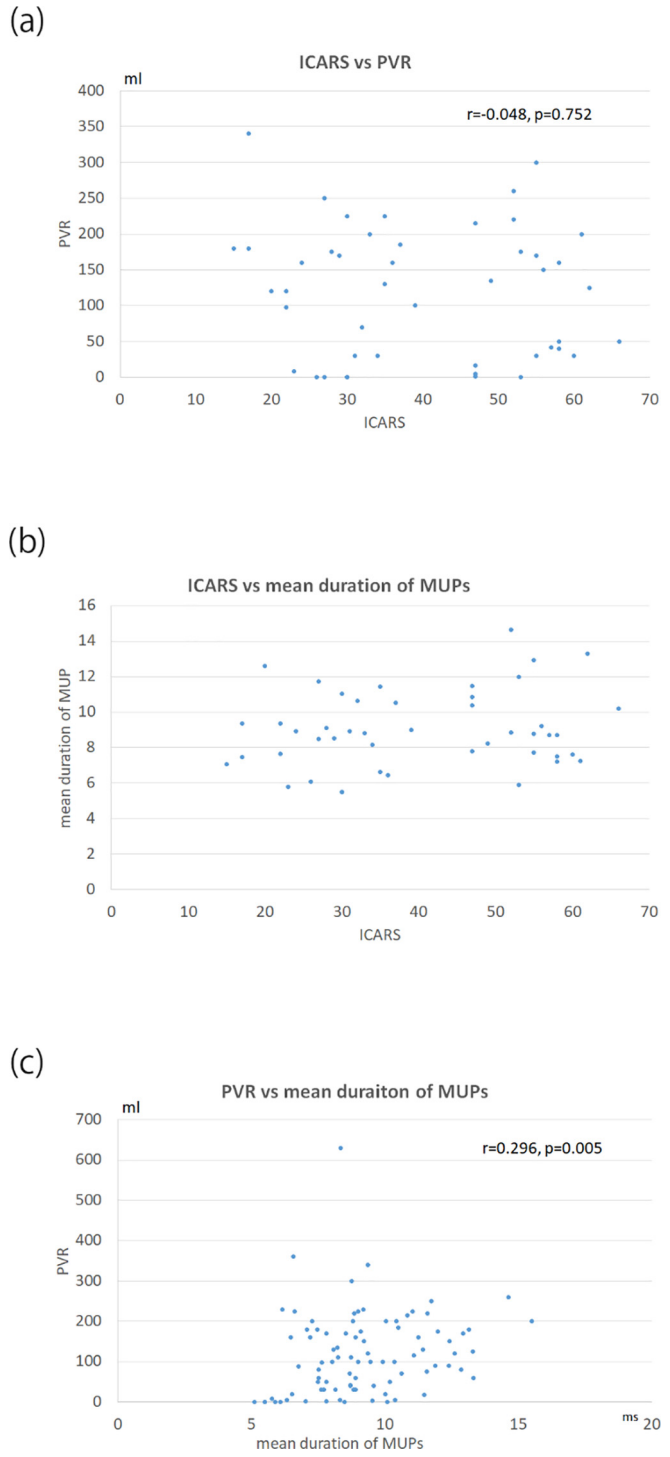

Fig. 2. Correlation between urodynamic parameters (PVR and mean duration of MUPs) and ICARS.
The correlation coefficient between ICARS and PVR was 0.093 (p = .539) (Fig. 2a), and between ICARS and mean duration of MUP in anal sphincter electromyography was 0.105 (p = .811) (Fig. 2b). The correlational coefficient between PVR and mean duration of MUP, 0.296, was significant (p = .005) (Fig. 2c).

The presence of urinary urgency, frequency or incomplete bladder emptying is required for the diagnosis of "possible MSA," and was present in this study. However, these symptoms are not specific to MSA and it is usually difficult to evaluate whether or not they are associated with MSA.

We have previously reported that the presence of large PVR in patients with motor dysfunctions strongly suggests the diagnosis of MSA, and measuring PVR is helpful in the differential diagnosis of MSA [10]. However, it is not uncommon that some patients with MSA do not have large PVR [11]. When large PVR is not detected, the presence of orthostatic hypotension is useful for the diagnosis of MSA. However, our previous report indicated that orthostatic hypotension was relatively mild in patients with MSA-C compared with those with MSA-P [7]. Urinary dysfunction is usually more common than orthostatic hypotension in the early stage of MSA.

We have shown that the initial symptom in 68% of patients with MSA-C was cerebellar ataxia [4], and it is not uncommon that autonomic dysfunction is mild in patients with MSA whose initial symptoms are motor dysfunction. With improved MRI, some patients with cerebellar ataxia are suspected of having MSA rather than pure cerebellar SCD even though their autonomic dysfunction may not meet the second consensus criteria of MSA. Since activities of daily living in MSA deteriorates at a more rapid rate than pure cerebellar SCD, it is important to inform patients and their caregivers of the potential for MSA as early as possible, even though their autonomic dysfunction may not yet meet the diagnostic criteria.

Remarkably, PVR and mean duration of MUPs in anal sphincter muscle had a positive significant correlation. Since large PVR is attributable to impaired bladder contraction, which is regulated by sacral parasympathetic neurons, and long mean duration of MUPs in anal sphincter muscle is caused by neurodegeneration of Onuf's nucleus located in the sacral cord, significant positive correlation between PVR and the mean duration of MUPs in the anal sphincter muscle suggests that degeneration of sacral parasympathetic neurons and Onuf's nucleus are correlated in MSA-C.

There has been little research examining the relationship between motor dysfunctions and urinary dysfunction in MSA. Although, urinary dysfunction is common and severe in MSA-C, the findings of the present study indicates that the severity of motor dysfunctions and urinary dysfunction was not correlated, and the diagnosis of MSA-C, especially with mild urinary dysfunction must be confirmed with caution.

The major limitation of this study is its cross-sectional and retrospective nature. A prospective and longitudinal examination of the relationship between motor dysfunctions and urinary dysfunction is desirable. Another limitation was that we evaluated motor dysfunctions only by ICARS score which is contaminated by parkinsonian features [12]. The additional evaluation of parkinsonism by UPDRS (Unified Parkinson's disease Rating Scale) or UMSARS (Unified Multiple System Atrophy Rating Scale) are desirable in our future study.

7. Conclusion

Motor and urinary dysfunction (urinary voiding dysfunction and neurogenic changes in sphincter EMG) are not correlated in MSA-C.

References

[1] A. Fanciulli, G.K. Wenning, Multiple-system atrophy, N. Engl. J. Med. 372 (3) (2015) 249–263, https://doi.org/10.1056/NEJMra1311488.
[2] I. Yabe, H. Soma, A. Takei, N. Fujiki, T. Yanagihara, H. Sasaki, MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA, J. Neurol. Sci. 249 (2) (2006) 115–121.
[3] H. Watanabe, Y. Saito, S. Terao, T. Ando, T. Kachi, E. Mukai, I. Aiba, Y. Abe, A. Tamakoshi, M. Doyu, M. Hirayama, G. Sobue, Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients, Brain. 125 (Pt 5) (2002) 1070–1083.
[4] T. Yamamoto, M. Asahina, Y. Yamanaka, T. Uchiyama, S. Hirano, A. Sugiyama, R. Sakakibara, S. Kuwabara, Urinary dysfunctions are more severe in the Parkinsonian phenotype of multiple system atrophy, Mov. Disord. Clin. Pract. 3 (3) (2016) 275–281, https://doi.org/10.1002/mdc3.12289.
[5] J.A. Palma, L. Norcliffe-Kaufmann, H. Kaufmann, Diagnosis of multiple system atrophy, Auton. Neurosci. 211 (2018) 15–25, https://doi.org/10.1016/j.autneu.2017.10.007.
[6] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, N.W. Wood, C. Colosimo, A. Dürr, C.J. Fowler, H. Kaufmann, T. Klockgether,

A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology. 71 (9) (2008) 670–676, https://doi.org/10.1212/01.wnl.0000324625.00404.15.

[7] R. Sakakibara, T. Hattori, T. Uchiyama, K. Kita, M. Asahina, A. Suzuki, T. Yamanishi, Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? J. Neurol. Neurosurg. Psychiatry 68 (1) (2000 Jan) 65–69.

[8] T. Yamamoto, R. Sakakibara, T. Uchiyama, Z. Liu, T. Ito, Y. Awa, T. Yamanishi, T. Hattori, Questionnaire-based assessment of pelvic organ dysfunction in multiple system atrophy, Mov. Disord. 24 (7) (2009) 972–978, https://doi.org/10.1002/mds.22332.

[9] T. Yamamoto, R. Sakakibara, T. Uchiyama, C. Yamaguchi, F. Nomura, T. Ito, M. Yanagisawa, M. Yano, Y. Awa, T. Yamanishi, T. Hattori, S. Kuwabara, Pelvic organ dysfunction is more prevalent and severe in MSA-P compared to Parkinson's disease, Neurourol. Urodyn. 30 (1) (2011) 102–107, https://doi.org/10.1002/nau.20948.

[10] T. Yamamoto, M. Asahina, Y. Yamanaka, T. Uchiyama, S. Hirano, M. Fuse, Y. Koga, R. Sakakibara, S. Kuwabara, Postvoid residual predicts the diagnosis of multiple system atrophy in Parkinsonian syndrome, J. Neurol. Sci. 381 (2017) 230–234, https://doi.org/10.1016/j.jns.2017.08.3262.

[11] T. Ito, R. Sakakibara, K. Yasuda, T. Yamamoto, T. Uchiyama, Z. Liu, T. Yamanishi, Y. Awa, K. Yamamoto, T. Hattori, Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? Mov. Disord. 21 (6) (2006) 816–823.

[12] F. Tison, F. Yekhlef, E. Balestre, V. Chrysostome, N. Quinn, G.K. Wenning, W. Poewe, Application of the international cooperative Ataxia scale rating in multiple system atrophy, Mov. Disord. 17 (6) (2002 Nov) 1248–1254.