Clinical Autonomic Research (2019) 29:627–631
https://doi.org/10.1007/s10286-018-0550-y

RESEARCH ARTICLE

Bladder dysfunction as the initial presentation of multiple system atrophy: a prospective cohort study

Ryuji Sakakibara[1,5] · Jalesh Panicker[2,5] · Sara Simeoni[2,5] · Tomoyuki Uchiyama[3,5] · Tatsuya Yamamoto[4,5] · Fuyuki Tateno[1,5] · Masahiko Kishi[1,5] · Yosuke Aiba[1,5]

Received: 12 April 2018 / Accepted: 16 July 2018 / Published online: 24 July 2018

Abstract

Objectives Multiple system atrophy (MSA) is a disease that combines autonomic (orthostatic or bladder) with motor [parkinsonian (MSA-P) or cerebellar (MSA-C)] dysfunction. While bladder dysfunction may occur earlier than motor disorders, thus far no prospective study has been available to determine how often and how early bladder autonomic dysfunction predates motor dysfunction in MSA. Therefore, we present data from detailed history-taking in patients with MSA.

Methods This is a prospective cohort study. Detailed history-taking was performed and a questionnaire administered in 121 MSA patients (73 MSA-C, 48 MSA-P; 74 men, 47 women; age, 58 ± 8.0 years; initial recruitment period, 5 years; follow-up, 6.5 ± 4.0 years).

Results Among the patients with MSA-C, 40 patients (55%) suffered motor dysfunction first, 22 (30%) suffered autonomic dysfunction first, and 11 (15%) initially suffered both simultaneously. Among the patients with MSA-P, 22 patients (46%) suffered motor dysfunction first, 22 (46%) suffered autonomic dysfunction first, and two (8%) initially suffered both simultaneously. Among the 'autonomic-first' subgroup of MSA-C patients, five suffered orthostatic dysfunction first, 13 suffered urinary dysfunction first, and four initially suffered both simultaneously. Among the 'autonomic-first' subgroup of MSA-P patients, six suffered orthostatic dysfunction first, nine suffered urinary dysfunction first, and seven initially suffered both simultaneously. Urinary symptoms were further preceded by erectile dysfunction in men. Overall, 18.2% of patients suffered only urinary symptoms initially, and the mean interval from the onset of urinary to the onset of motor symptoms was 2.8 years (range 1–7 years).

Conclusion In MSA patients, 18.2% presented with bladder dysfunction as the sole initial manifestation, and the mean interval from the onset of urinary to the onset of motor symptoms was 2.8 years. It is clinically important to avoid unnecessary prostatic surgery when MSA patients see urologists before neurologists.

Keywords Multiple system atrophy · Autonomic dysfunction · Urinary dysfunction · Prostatic hypertrophy · Nonmotor signs

Introduction

Multiple system atrophy (MSA) is clinically characterized by a combination of autonomic (orthostatic and/or bladder) and motor (parkinsonian and/or cerebellar) disorders [1–3]. Among the autonomic disorders, orthostatic hypotension is observed in Parkinson's disease (PD) [4, 5] but urinary retention is not observed in PD; therefore, in the context of motor dysfunction, it is a distinguishing feature of MSA [2, 3]. However, there is a concern that bladder dysfunction occurs earlier than motor disorder. In that situation, men with MSA may see urologists before the diagnosis of MSA has been made [6, 7] and may then undergo prostatic surgery

✉ Ryuji Sakakibara
sakakibara@sakura.med.toho-u.ac.jp

1 Neurology, Internal Medicine, Sakura Medical Center, Toho University, 564-1 Shimoshizu, Sakura 285-8741, Japan

2 Uro-Neurology, The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, Queen Square, London, UK

3 Continence Center, Dokkyo Medical College, Tochigi, Japan

4 Neurology, Chiba University, Chiba, Japan

5 Urology, Sakura Medical Center, Toho University, Sakura, Japan

following a diagnosis of prostatic hyperplasia. This surgical outcome is unfavorable because of the progressive nature of MSA [6]. However, thus far, no prospective study has been available to determine how often and how early bladder autonomic dysfunction predates motor disorder in MSA. In order to answer this question, here we present data from detailed history-taking in patients with MSA.

Methods

Patients and motor/autonomic history-taking

The study reported here was an in-depth analysis of our previous report [8], which was a prospective cohort study (recruitment period, 5 years; prospective follow-up period, 6.5 ± 4.0 years [mean ± standard deviation, visit at least once a year, followed by movement disorder specialists, autonomic (covering cardiovascular, urinary/bowel, and sleep apnea) specialists, and urologists together]; 121 MSA patients; 73 with MSA-C (cerebellar form, common in Japan [9]), 48 with MSA-P (parkinsonian form); the inclusion and exclusion criteria conformed to the second consensus statement on the diagnosis of MSA [1]; 74 men, 47 women; age 58 ± 8.0 years; no autopsy). At the first visit, all patients were subjected to a standard neurological examination and brain magnetic resonance imaging (MRI) and were administered an autonomic questionnaire. In addition, we performed ^{123}I metaiodobenzylguanidine (MIBG) myocardial scintigraphy [10], measured alpha-synuclein in the cerebrospinal fluid [11], and carried out gene analysis in some patients in order to exclude dementia with Lewy bodies, pure autonomic failure (mostly with Lewy body pathology), hereditary cerebellar ataxia, and other diseases that may mimic MSA [12]. All patients met the criteria of probable MSA during the course of the disease according to the abovedescribed brain/heart imaging and sacral cord tests (open bladder neck and sphincter EMG), particularly those who initially suffered from an autonomic disorder only. The diagnosis was confirmed again at the final follow-up (Figs. 1, 2).

The autonomic questionnaire covered orthostatic symptoms (including faintness, blurred vision, and syncope; we devised a cardiovascular questionnaire, not validated) [5, 8], lower urinary tract (LUT) symptoms (LUTS) [Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom Score (IPSS), including nocturnal and diurnal urinary frequency, sensation of urgency, urinary incontinence; voiding difficulty and retention], and erectile dysfunction [five-item International Index of Erectile Function (IIEF-5)]. In order to clarify the timeline, we performed detailed history-taking from patients concerning urinary, orthostatic, erectile (men), and gait/motor dysfunction. None had abnormalities in the electrocardiogram, chest roentgenogram, blood chemistry (including blood sugar), urinalysis, or abdominal ultrasonography (including kidney and prostate). At the first visit, we performed objective autonomic function tests in all patients [8]. Cardiovascular tests included the head-up tilt test, measurement of supine plasma noradrenaline (NA), measurement of R–R variability (CV R–R), and intravenous infusions of NA (for alpha receptors) and isoproterenol (for beta receptors) (denervation supersensitivity of the vessel). Urodynamic studies comprised measurement of post-micturition residuals, EMG-cystometry,

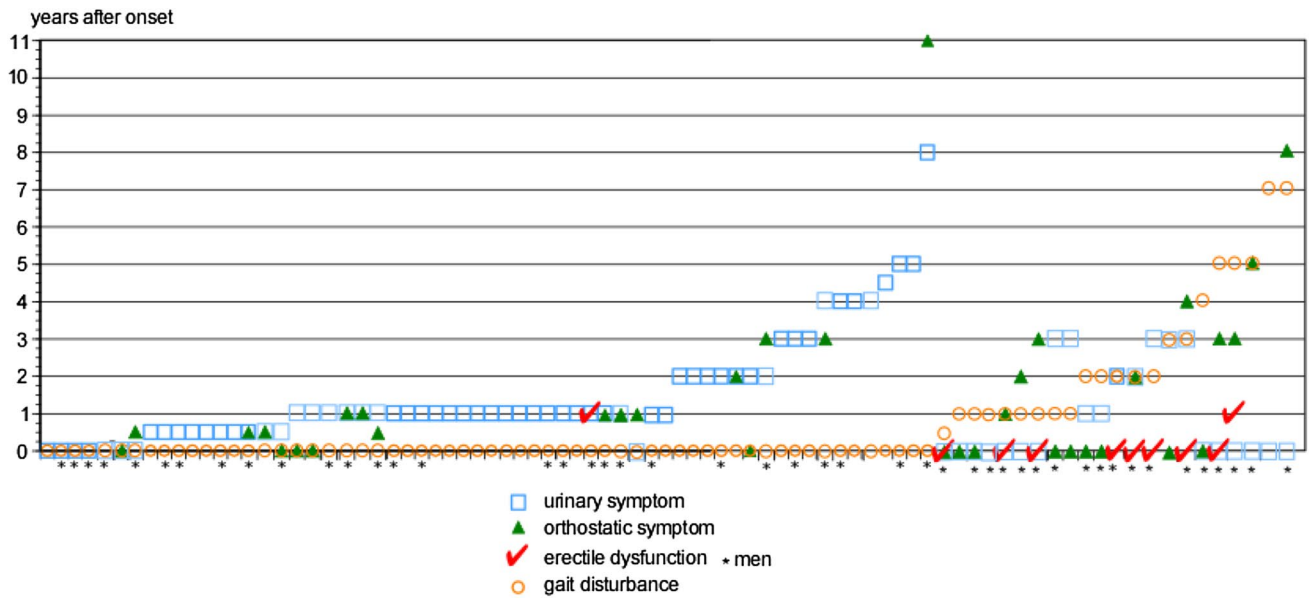

Fig. 1 Appearance of four major symptoms in MSA-C (multiple system atrophy—cerebellar form). Please see text

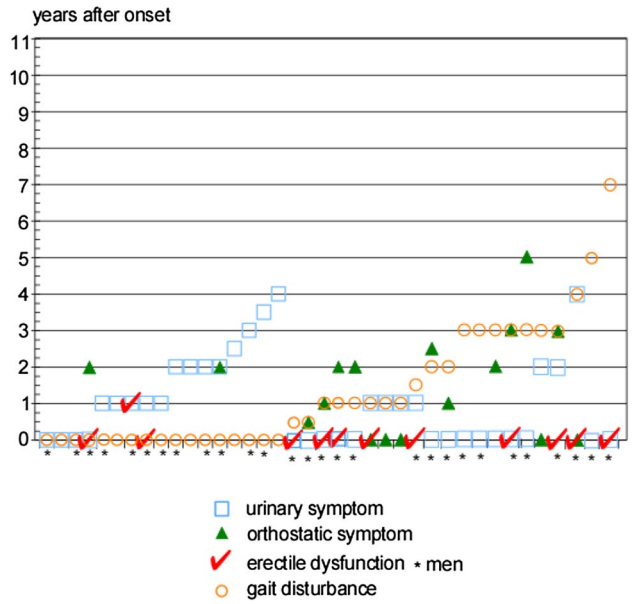

Fig. 2 Appearance of four major symptoms in MSA-P (multiple system atrophy—parkinsonian form). Please see text

and bethanechol (for Ach receptors) subcutaneous injection (denervation supersensitivity of the bladder). Orthostatic hypotension (systolic pressure below − 30 mmHg or diastolic pressure below − 15 mmHg) was noted in 41%. Various bladder dysfunctions were noted in 96% of the patients. Among these, post-void residuals (PVRs) were noted in 74% of patients. EMG-cystometry showed detrusor overactivity in 56%, low compliance in 31%, an atonic curve in 5%, detrusor sphincter dyssynergia in 45%, and a neurogenic sphincter EMG in 74%. Bethanechol injection showed denervation supersensitivity of the bladder in 19%. We started patients with PVR > 100 ml on clean, intermittent catheterization, as performed by the patients themselves and their caregivers. When nocturnal polyuria was a problem, we also taught them to use an Intermittent Night Balloon (DIB International Co., Ltd.). When incontinence/severe urgency was a problem, we gave them anticholinergics/beta-3 receptor agonists. No significant urological infection or kidney dysfunction was observed. Other data were shown previously [8]. Statistics were analyzed via Student's *t* test. All patients gave their informed consent before participating in the study. This study was approved by the university ethics committee, and conformed to the Declaration of Helsinki.

Results

At the first visit, among the patients with MSA-C ($n = 73$), neurological examination and the autonomic questionnaire showed urinary symptoms in all (100%), orthostatic symptoms in 35 (48%), erectile dysfunction in 10/36 men (28%), and cerebellar ataxia/gait difficulty in all (100%). Similarly, among the patients with MSA-P ($n = 48$), urinary symptoms were noted in all (100%), orthostatic symptoms in 17 (23%), erectile dysfunction in 12/38 men (32%), and parkinsonism/gait difficulty in all (100%). Therefore, urinary symptoms were more common than orthostatic symptoms in both MSA-C ($p = 0.008$) and MSA-P ($p = 0.009$) patients.

Also, among the patients with MSA-C ($n = 73$), 40 patients (55%) suffered motor dysfunction first, 22 (30%) suffered autonomic dysfunction first, and 11 (15%) initially suffered both motor and autonomic symptoms simultaneously. Among the patients with MSA-P ($n = 48$), 22 (46%) suffered motor dysfunction first, 22 (46%) suffered autonomic dysfunction first, and two (8%) initially suffered both motor and autonomic dysfunction simultaneously. Among the 'autonomic-first' MSA-C patients, five suffered orthostatic dysfunction first, 13 suffered urinary dysfunction first, and four initially suffered orthostatic and urinary dysfunction simultaneously. Urinary symptoms were further preceded by erectile dysfunction in men (in four patients, erectile dysfunction was the sole initial symptom). Similarly, among the 'autonomic-first' MSA-P patients, six suffered orthostatic dysfunction first, nine suffered urinary dysfunction first, and seven initially suffered both orthostatic and urinary dysfunction simultaneously. Urinary symptoms were also preceded by erectile dysfunction in men (erectile dysfunction was the sole initial symptom in two patients).

Overall, 22 patients (18.2%; 13 MSA-C, 9 MSA-P) initially suffered urinary symptoms but not orthostatic or cerebellar/parkinsonian symptoms. In those patients, the mean interval from the onset of urinary to the onset of motor symptoms was 2.8 years (range 1–7 years).

Discussion

Previously, it was unclear how often and how early bladder autonomic dysfunction predates motor disorder in MSA. To our knowledge, this is the first prospective cohort study to investigate that question. We found that (i) 18.2% of MSA patients presented with bladder dysfunction as the sole initial manifestation and (ii) the mean interval from the onset of urinary to the onset of motor symptoms was 2.8 years (1–7 years). The exact reasons for these findings remain unclear. However, bladder dysfunction, particularly urinary retention in MSA, may reflect pathology in the sacral cord (as discussed below), which is a common site for lesions in MSA [1]. Therefore, it is reasonable to assume that in such 'bladder-first' cases of MSA, the sacral cord may have been affected earlier in the course of disease.

The above findings are important not only from an academic perspective but also from the point of view of patient care [13]. Although such cases have hitherto been

underrecognized, MSA is a more aggressive degenerative disorder than PD. Surgical treatment of bladder outlet obstruction often fails in MSA patients and should be avoided, whereas prostatic surgery is not contraindicated in patients with PD [13]. In addition, 'bladder-first' cases are extremely rare in PD patients [14].

The autonomic questionnaire showed erectile dysfunction in 10/36 men (28%) with MSA-C and 12/38 men (32%) with MSA-P, often predating urinary symptoms in both subgroups. The rate of erectile dysfunction in the present study is actually lower than the previously reported rate [15]. We do not know the exact reason for this. However, it may be due to differences in sexual activity in Japan, the questionnaire we used, or differences in underreporting rates. The questionnaire also showed that orthostatic symptoms predated motor disorder in five MSA-C patients and in six MSA-P patients. Cases of pure autonomic failure (PAF), most of whom have Lewy body pathology, also show orthostatic hypotension [4]. Therefore, we performed additional tests (MIBG myocardial scintigraphy and MRI) to confirm the diagnosis of MSA. We did not include laryngeal stridor in the questionnaire; therefore, the occurrence of laryngeal stridor in our cohort remains unknown. However, it was reported that laryngeal abductor paralysis was an early, solitary manifestation in 4% of MSA cases, and may further predate bladder dysfunction [16].

This study was performed by movement disorder specialists, autonomic (i.e., cardiovascular, urinary/bowel, and sleep apnea) specialists, and urologists together at our university clinic. Nevertheless, there may still be a bias from a higher incidence (18.2%) of MSA patients who initially suffered bladder dysfunction only in this study than encountered in other institutes.

How to recognize patients who should not have urological surgery at a urology clinic [13, 17, 18]

From a uro-neurological perspective, there are three urologic features of MSA. The first is a large post-void residual urine volume of > 100 ml (by ultrasound; < 20 ml by ultrasound is normal) without prostatic hyperplasia in men and without common neurologic conditions (lumbar spondylosis and diabetes) [19, 20]. The post-void residual urine volume in MSA requires measurement and particular attention. This is because a large post-void residual urine volume may result in recurrent urinary tract infection and may cause morbidity. Urinary incontinence results in impaired self-esteem, stress on caregivers, and considerable financial cost. The second feature is an open bladder neck during filling-phase videourodynamics, as reported previously [2, 3], which is not uncommon in stress-incontinent women but is extremely rare in men. These two tests can be performed at a urology clinic. The third feature is sphincter electromyography (EMG) abnormality, i.e., neurogenic motor unit potentials [2]. A distinguishing pathology in MSA is neuronal cell loss in Onuf's nucleus (a group of anterior horn cells in the sacral spinal cord), which may start early in the course of MSA [17, 21]. The first report of neurogenic changes in external anal sphincter (EAS)-EMG in MSA was attributed to Sakuta et al. in [22, 23, 24]. Since then, EAS-EMG results for over 600 MSA patients have been reported, with abnormality rates of > 70% observed in several studies [23, 24]. EAS-EMG is better tolerated and yields results identical to those from external urethral sphincter investigations. EAS-EMG abnormality rates are similar for MSA-P and MSA-C patients [20]. Abnormalities have also been recorded in the bulbocavernosus muscle in MSA. For most neurologists, sphincter EMG is easy to perform and interpret in clinical practice. It is particularly important not to overlook the late components (satellite potentials). Although sphincter EMG abnormalities are noted in some patients with PD, dementia with Lewy bodies, pure autonomic failure, and progressive supranuclear palsy [23, 25], it is highly recommended that the diagnoses of early MSA patients should be examined via sphincter EMG in future studies.

In conclusion, 18.2% of the MSA patients presented with bladder dysfunction as the sole initial manifestation, and the mean interval from the onset of urinary to the onset of motor symptoms was 2.8 years (1–7 years). It is clearly important to avoid unnecessary prostatic surgery when MSA patients see urologists before neurologists.

Acknowledgements We cordially thank Prof. Niall Quinn in Queen Square, London for his valuable suggestions.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

References

1. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71:670–676
2. Sakakibara R, Tateno F, Yamamoto T, Uchiyama T, Yamanishi T (2018) Urological dysfunction in synucleinopathies: epidemiology, pathophysiology and management. Clin Auton Res 28:83–101
3. Ogawa T, Sakakibara R, Kuno S, Ishizuka O, Kitta T, Yoshimura N (2017) Prevalence and treatment of LUTS in patients with Parkinson disease or multiple system atrophy. Nat Rev Urol 14:79–89
4. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, Biaggioni I, Low PA, Singer W, Goldstein DS, Peltier AC, Shibao CA, Gibbons CH, Freeman R, Robertson D, Autonomic Disorders Consortium (2017) Natural history of pure autonomic failure: a United States prospective cohort. Ann Neurol 81:287–297

5. Sakakibara R, Hattori T, Uchiyama T, Asahina M, Yamanishi T (2000) Micturitional disturbance in pure autonomic failure. Neurology 54:499–501
6. Magari T, Fukabori Y, Ogura H, Suzuki K (2013) Lower urinary tract symptoms of neurological origin in urological practice. Clin Auton Res 23:67–72
7. McKay JH, Cheshire WP (2018) First symptoms in multiple system atrophy. Clin Auton Res 28:215–221. https://doi.org/10.1007/s10286-017-0500-0
8. Sakakibara R, Hattori T, Uchiyama T, Kita K, Asahina M, Suzuki A, Yamanishi T (2000) Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? J Neurol Neurosurg Psychiatry 68:65–69
9. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, Aiba I, Abe Y, Tamakoshi A, Doyu M, Hirayama M, Sobue G (2002) Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 125:1070–1083
10. Sakakibara R, Tateno F, Kishi M, Tsuyusaki Y, Terada H, Inaoka T (2014) MIBG myocardial scintigraphy in pre-motor Parkinson's disease: a review. Parkinson Relat Disord 20:267–273
11. Tateno F, Sakakibara R, Kawai T, Kishi M, Murano T (2012) Alpha-synuclein in the cerebrospinal fluid differentiates synucleinopathies (Parkinson disease, dementia with Lewy bodies, multiple system atrophy) from Alzheimer disease. Alzheimer Dis Assoc Disord 26:213–216
12. Palma JA, Norcliffe-Kaufmann L, Kaufmann H (2017) Diagnosis of multiple system atrophy. Auton Neurosci 211:15–25. https://doi.org/10.1016/j.autneu.2017.10.007
13. Sakakibara R, Panicker J, Finazzi-Agro E, Iacovelli V, Bruschini H, Parkinson's Disease Subcommittee, The Neurourology Promotion Committee in The International Continence Society (2016) A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn 35:551–563
14. Takahashi O, Sakakibara R, Tateno F, Kishi M, Tsuyusaki Y, Aiba Y, Yano H, Sugiyama M, Yamamoto T, Yamanishi T, Uchiyama T, Shibata C, Tomaru T (2014) Overactive bladder may precede motor disorder in Parkinson's disease: a urodynamic study. Parkinson Relat Disord 20:1030–1032
15. Tandon R, Pradhan S (2015) Autonomic predominant multiple system atrophy in the context of Parkinsonian and cerebellar variants. Clin Neurol Neurosurg 130:110–113
16. Uzawa A, Sakakibara R, Tamura N, Asahina M, Yamanaka Y, Uchiyama T, Ito T, Yamamoto T, Liu Z, Hattori T (2005) Laryngeal abductor paralysis can be a solitary manifestation of multiple system atrophy. J Neurol Neurosurg Psychiatry 76:1739–1741
17. Chandiramani VA, Palace J, Fowler CJ (1997) How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol 80:100–104
18. Köllensperger M, Geser F, Seppi K, Stampfer-Kountchev M, Sawires M, Scherfler C, Boesch S, Mueller J, Koukouni V, Quinn N, Pellecchia MT, Barone P, Schimke N, Dodel R, Oertel W, Dupont E, Østergaard K, Daniels C, Deuschl G, Gurevich T, Giladi N, Coelho M, Sampaio C, Nilsson C, Widner H, Sorbo FD, Albanese A, Cardozo A, Tolosa E, Abele M, Klockgether T, Kamm C, Gasser T, Djaldetti R, Colosimo C, Meco G, Schrag A, Poewe W, Wenning GK, European MSA Study Group (2008) Red flags for multiple system atrophy. Mov Disord 23:1093–1099
19. Yamamoto T, Asahina M, Yamanaka Y, Uchiyama T, Hirano S, Fuse M, Koga Y, Sakakibara R, Kuwabara S (2017) The utility of post-void residual volume versus sphincter electromyography to distinguish between multiple system atrophy and Parkinson's disease. PLoS One 12(1):e0169405. https://doi.org/10.1371/journal.pone.0169405 **(eCollection 2017)**
20. Yamamoto T, Sakakibara R, Uchiyama T, Liu Z, Ito T, Awa Y, Yamamoto K, Kinou M, Yamanishi T, Hattori T (2005) When is Onuf's nucleus involved in multiple system atrophy? A sphincter electromyography study. J Neurol Neurosurg Psychiatry 76:1645–1648
21. Coon EA, Cutsforth-Gregory JK, Benarroch EE (2018) Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord 33:349–358. https://doi.org/10.1002/mds.27186
22. Sakuta M, Nakanishi T, Toyokura Y. Anal muscle electromyograms differ in amyotrophic lateral sclerosis and Shy-Drager syndrome. Neurology. 1978;28:1289–1293
23. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M (2009) Sphincter EMG as a diagnostic tool in autonomic disorders. Clin Auton Res 19:20–31
24. Hoeritzauer I, Phé V, Panicker JN (2016) Urologic symptoms and functional neurologic disorders. Handb Clin Neurol 139:469–481
25. Tateno F, Sakakibara R, Ogata T, Kishi M, Tsuyusaki Y, Takahashi O, Sugiyama M, Tateno A (2015) Lower urinary tract function in dementia with Lewy bodies (DLB). Mov Disord 30:411–415