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【 CASE REPORT 】

Female Urinary Retention Progressing to Possible Multiple System Atrophy-cerebellar Form after 12 Years

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Abstract:
We herein report a 73-year-old Japanese woman with possible multiple system atrophy-cerebellar form (MSA-C) who suffered from urinary retention (sacral autonomic disorder) for 12 years before exhibiting cerebellar ataxia. A peculiar combination of findings on urodynamics and sphincter electromyography (EMG), e.g. detrusor hyperactivity with impaired contraction (DHIC), detrusor-sphincter dyssynergia (DSD) and neurogenic sphincter EMG (upper and lower neuron-type autonomic dysfunction), seems to have been predictive of future development of MSA.

Key words: multiple system atrophy, sacral autonomic disorder, urinary retention, sphincter electromyography, magnetic resonance imaging

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Introduction

Multiple system atrophy (MSA) is a progressive degenerative neurological disorder, pathologically characterized by glial cytoplasmic inclusions that are alpha-synuclein (α-Syn)-positive. MSA is clinically defined as a combination of motor [parkinsonian MSA (MSA-P) and/or cerebellar MSA (MSA-C)] and autonomic (orthostatic and/or bladder) disorders by the second consensus statement on the diagnosis of MSA (1). Recent prospective cohort studies have shown that up to 18.2% of MSA patients start with bladder dysfunction as the only presenting symptom for up to 7 years (2-4), suggesting that the disease process of alpha-synuclein aggregation might begin in the sacral spinal cord (5, 6).

Thus far, there have been no reports of MSA-C patients with bladder dysfunction as the only symptom for more than seven years. Recently, however, we encountered a woman with possible MSA-C who experienced female urinary retention for 12 years before starting to exhibit cerebellar ataxia.

Case Report

A 60-year-old, previously healthy Japanese woman with no family history gradually developed lower urinary tract symptoms. Symptoms of overactive bladder (urinary urgency, daytime frequency of nine times, night-time frequency of twice, occasional urge urinary incontinence) gradually began to overlap with those of difficult urination: poor stream, intermittent voiding, and sensation of post-void residual (PVR). She visited local urology clinics, but no abnormalities were found. She was also referred to local neurology clinics, again with no significant findings. At 63 years old, her difficult urination worsened; she was able to void only 50 mL of urine voluntarily, leaving a large PVR volume of 500 mL. She was taught to perform clean, intermittent self-catheterization (CIC) six times a day. At 70

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years old, she visited a urogynecology clinic, where her symptoms were suspected to have a neurogenic etiology because of her state of quasi-complete female urinary retention. She had no difficulty with defecation, reporting a bowel movement once every two days, without a laxative. She did not respond to a sexual questionnaire and had no history of motor disorder.

At 71 years old, she was referred to us by her urogynecologist to search for neurological etiologies again. She was alert, active and cooperative. She had no dementia. She had slight neurotic features but no history of psychiatric medication. Her cranial nerve functions, including extraocular movement, speech, and facial expression, were normal. She had no parkinsonism, including tremor, akinesia, or rigidity, even in response to an inducing maneuver. She also had no cerebellar ataxia with respect to coordination (finger-to-nose test, finger-to-ear test, diadochokinesis), stance, tandem gait, or turning. The Romberg sign was negative. She had no motor paresis. Deep tendon reflexes were normal in all four extremities, and she had flexor extensor plantar responses. Sensations were normal including the sacral area. She had no dimple or café-au-lait spots around the sacral area. She had no history of rapid-eye movement (REM) sleep behavioral disorder or sleep apnea. She had no constipation. She had no history of postural dizziness suggesting orthostatic hypotension (she was not willing to undergo the head-up tilt test). She did not have anhidrosis.

Blood test and urinalysis results were all normal, with no signs of diabetes or kidney disease. Nerve conduction study results were normal. Previous brain magnetic resonance imaging (MRI) scans had been normal. ^{99m}Tc-L,L-ethylcysteinate dimer-single-photon emission computed tomography (ECD-SPECT) and ^{123}I-ioflupane (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane) dopamine transporter (DAT) scan showed normal findings. Lumbar MRI findings were normal. She was not willing to undergo any other tests.

At 71 years old, urodynamics-sphincter electromyography (EMG) was performed using the International Continence Society method (7). Free-flow was not obtained. During slow filling, she had detrusor overactivity (Fig. 1A, arrows). During voiding, she had detrusor-sphincter dyssynergia (DSD). She voided 20 mL and left a large PVR volume of 280 mL. A pressure-flow analysis revealed outlet obstruction in addition to detrusor underactivity (Fig. 1B). An analysis of the sphincter EMG findings revealed that 50% of motor unit potentials were abnormal (duration >10 ms), indicating external sphincter denervation (normal <20%) (Fig. 1C). In summary, she had a peculiar combination of findings on urodynamics and sphincter EMG, namely detrusor hyperactivity with impaired contraction (DHIC) (2, 8), DSD and neurogenic sphincter EMG (upper and lower neuron-type autonomic dysfunction). However, no neurological diseases were discovered at that time. We, along with her urogynecologist, started to follow her very carefully, suspecting a 'masked' neurological disease.

One year later, at 72 years old, she reported that she had developed trouble walking down the stairs, with 3 unexpected falls having occurred. One year after that, at 73 years old, she was referred to us again. On an examination, she was revealed to have difficulty in coordination (finger-to-nose test, finger-to-ear test, diadochokinesis), stance and turning (wide-based) and was unable to perform tandem gait, all signs of cerebellar ataxia. Her Romberg sign was still negative. She had no parkinsonism, constipation or postural dizziness. We did not inquire about sexual dysfunction. Other etiologies for cerebellar ataxia, including cerebellar strokes, infections, autoimmune diseases, toxic causes, alcohol, drugs, vitamin deficiencies and hypothyroidism, were excluded. We did not perform a gene analysis. The axial, sagittal and coronal planes of T2-weighted images of 3T MRI showed atrophy in the cerebellar vermis and cerebellar hemisphere, although midline linear hyperintensity or middle cerebellar peduncle hyperintensity was not observed (Fig. 2). All of these features suggested MSA-C (1-4). We are now following her carefully.

Discussion

Reportedly, up to 18.2% of MSA patients may have bladder dysfunction alone for up to a 7 year-period prior to the onset (2, 3). Thus far, however, there have been no reports of MSA-C patients presenting with bladder dysfunction as the sole symptom for more than seven years. To our knowledge, this is the first such case in which sacral autonomic disorder persisted for 12 years before cerebellar ataxia appeared.

Our case raises two clinical issues. The first issue is the uro-neurological differential diagnosis. Urinary retention has a variety of etiologies, both urologic and neurologic. Urologic etiologies are typically characterized by outlet obstruction, including a posterior urethral valve in young adults (9), benign prostate hypertrophy in men (10), postsurgical pelvic organ prolapse in women and large uterine leiomyoma in women (11). With the exception of Fowler's syndrome, neurologic etiologies typically involve detrusor underactivity, such as meningitis-retention syndrome, lumbar spondylosis and diabetic neuropathy (12, 13). None of these diseases were found in our case.

However, our patient did have DHIC. Among the two components of DHIC, detrusor overactivity during filling occurs in both MSA and Parkinson's disease (PD), while detrusor underactivity during voiding is typically seen in MSA (14-16). She had urinary retention (a large PVR volume of 280-500 mL), which is not seen in PD and is suggestive of MSA (14-16). She also had DSD and sphincter EMG abnormality (neurogenic motor unit potentials), which are not seen in PD and are suggestive of MSA (2, 3, 17). However, it is worth mentioning that one of these objective signs alone is not sufficient to diagnose MSA (16). In contrast, our patient showed a peculiar combination of findings on urodynamics and sphincter EMG [e.g. DHIC, DSD and

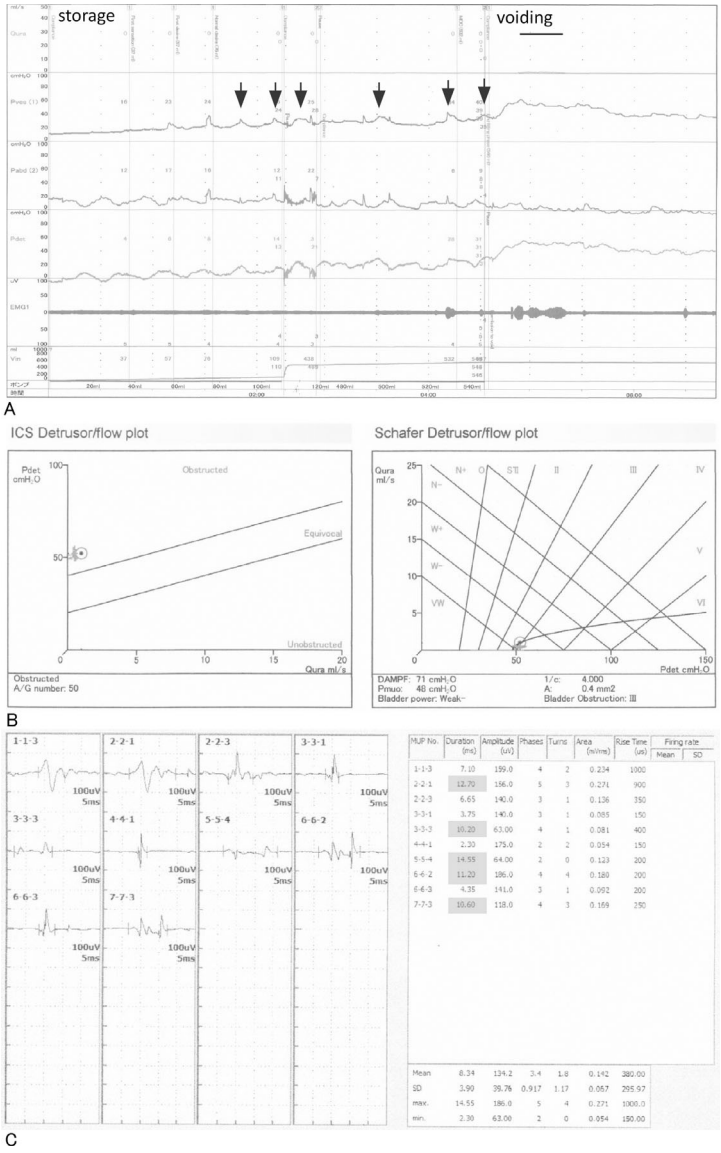

Figure 1. **Urodynamic and sphincter EMG tests 11 years after the first appearance of her lower urinary tract symptoms but before cerebellar ataxia or parkinsonism developed. A: During slow filling (50 mL/min), she reported her first sensation at 36 mL (100 mL<normal<300 mL) and normal desire to void at 75 mL. When she had a maximum desire to void (bladder capacity) at a volume of 260 mL (200 mL<normal<600 mL), we stopped infusing saline into the bladder. During this time, she showed phasic detrusor overactivity (arrows). Her abdominal pressure varied periodically, suggesting spontaneous periodic rectal contraction (SPRC) due to stool. During voiding, the sphincter EMG sounds increased in amplitude, suggesting detrusor-sphincter dyssynergia (DSD). She voided 20 mL and left a large PVR volume of 280 mL (normal<30 mL) (bladder volume 300 mL=infused volume plus diuresis volume). B: A pressure-flow analysis revealed obstruction, with a Schafer obstruction grade of 3 [numerically indicating the grade of bladder outlet (the prostate gland/urethra) obstruction, normal<1, 2=equivocal, 3-6 obstruction], and detrusor underactivity, with a Schafer contraction grade of "weak" (numerically indicating the grade of bladder contraction, 4 grades: strong, normal, weak, very weak) and a maximum Watts factor of 5.4 W/m^2 (also numerically indicating the grade of bladder contraction, normal>10 W/m^2). Based on these results, she was considered to have detrusor hyperactivity with impaired contraction (DHIC), together with an obstructive component (DSD). C: An analysis of the sphincter EMG revealed that 50% of motor unit potentials were abnormal (duration>10 ms), indicating external sphincter denervation (normal<20%). Decelerating burst/complex repetitive discharge was not observed. PVR: post-void residual, Flow: urinary flow, Pves: vesical (bladder) pressure, Pabd: abdominal (rectal) pressure, Pdiff: differential detrusor pressure=Pves-Pabd, EMG: electromyography**

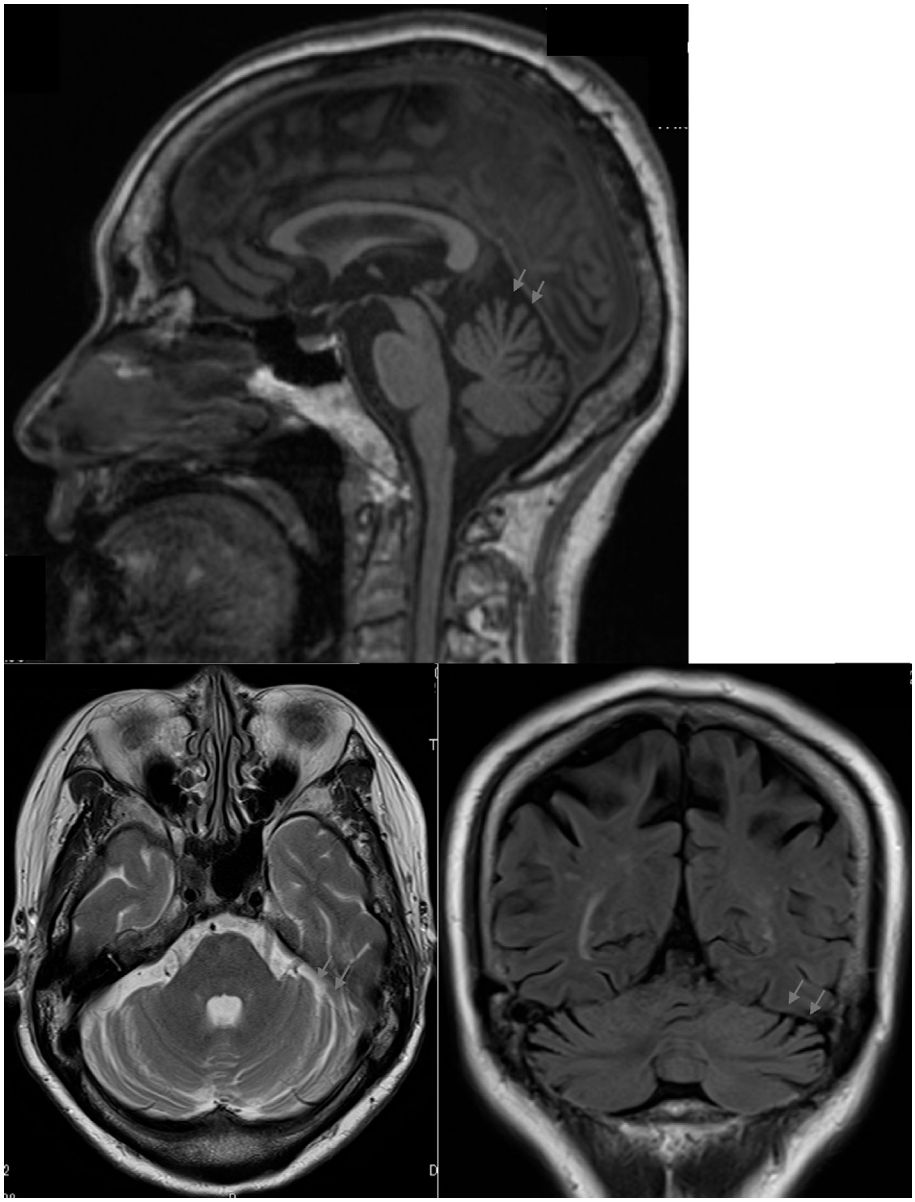

Figure 2. Brain MRI findings of the patient two years after the urodynamic tests. Axial, sagittal and coronal planes of T2-weighted 3T MRI showed atrophy in the cerebellar vermis and cerebellar hemisphere (arrows), although midline linear hyperintensity or middle cerebellar peduncle hyperintensity was not observed. She had no parkinsonism.

neurogenic sphincter EMG (upper and lower neuron-type autonomic dysfunction)]. If this finding is noted in young adults, we should check for spina bifida occulta (13); in adults, we should consider MSA (2). In our case, this finding seems to have been predictive of the future development of MSA.

The second issue is the clinical courses of synucleinopathies, namely PD and MSA. It is well described that Lewy body disease (LBD, with PD pathology) may present with pure autonomic failure (18). For example, Yamanaka et al. reported 2 cases, a 65-year-old man and a 74-year-old man (19), in whom orthostatic hypotension (with mild overactive bladder symptom but without voiding difficulty/retention) persisted for 11-12 years before the development of parkinsonian motor disorder and dementia, with a diagnosis of LBD made. Thus, periarterial autonomic disorder can be the very early, sole (non-motor) manifestation of LBD for more than 10 years. Synuclein pathology evidently starts at the periarterial nerves in some patients with LBD (18). Other initial non-motor features of LBD include REM sleep behavior disorder (20), constipation (21), anosmia (22), and dementia (mild cognitive impairment) (23). In such cases, α-Syn pathology may also start at a specific site in some patients with LBD. Among these, the bowel has been extensively studied in both experimental settings and human subjects. It has been shown that 1) environmental toxins (particularly pesticides in rural regions) may change microbiota (bacterial flora) in the bowel, triggering myenteric α-Syn pathology and the development of constipation in epidemiological and experimental studies (24); and 2) once α-Syn

pathology starts in the myenteric plexus, aggregated α-Syn may be able to be transmitted (like prion) from neuron to neuron, spreading to the brain through sympathetic (thoracic and lumbar sympathetic trunk) and parasympathetic (vagal and pelvic) nerves (25).

Similarly, given the present findings, sacral autonomic disorder may be the very early, sole (non-motor) manifestation of MSA for more than 10 years. This suggests that the synuclein pathology might start at the sacral spinal cord in some patients with MSA (5, 6). Other initial non-motor features of MSA include REM sleep behavior disorder (20), vocal cord paralysis (26) and anhidrosis (27). In such cases, the synuclein pathology may also start at a specific site in some patients with MSA. However, in contrast to LBD, few studies have focused on how propagation of α-Syn occurs in the neuraxis of MSA. Recent studies have indicated that 1) bladder dysfunction does occur in a transgenic mouse model of MSA (28); 2) α-Syn-preformed fibrils injected in the urethral sphincter or the bladder in transgenic mice initiate prion-like transmission of pathological α-Syn from the urogenital tract to the brain via micturition reflex pathways (29); and 3) in MSA, the α-Syn-containing beta-sheet structure seems milder and the spreading speed slower than in LBD/PD (30, 31).

Several limitations associated with the present study warrant mention. We performed imaging using only MRI (midline linear hyperintensity or middle cerebellar peduncle hyperintensity were not observed), perfusion SPECT, and DAT. We did not measure alpha-synuclein in the cerebrospinal fluid. We also did not perform a gene analysis in our patient. Therefore, other etiologies could not be completely excluded, so our patient was diagnosed only with 'possible' MSA-C. However, recognizing sacral autonomic disorder is important for patient care and the early initiation of disease-modifying therapy for MSA (31, 32). Therefore, further studies with a larger number of patients are warranted.

In conclusion, we encountered a 73-year-old Japanese woman with possible MSA-C who presented with female urinary retention (sacral autonomic disorder) as the sole symptom for 12 years before exhibiting cerebellar ataxia. A peculiar combination of findings on urodynamics and sphincter EMG, e.g. DHIC, DSD and neurogenic sphincter EMG (upper and lower neuron-type autonomic dysfunction), seems to be predictive of future development of MSA.

The authors state that they have no Conflict of Interest (COI).

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