

# Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation?

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## Abstract

**Objectives**—Urinary dysfunction and orthostatic hypotension are the prominent autonomic features in multiple system atrophy (MSA). A detailed questionnaire was given and autonomic function tests were performed in 121 patients with MSA concerning both urinary and cardiovascular systems.

**Methods**—Replies to the questionnaire on autonomic symptoms were obtained from 121 patients including three clinical variants; olivopontocerebellar atrophy (OPCA) type in 48, striatonigral degeneration (SND) type in 17, and Shy-Drager type in 56. Urodynamic studies comprised measurement of postmicturition residuals, EMG cystometry, and bethanechol injection. Cardiovascular tests included head up tilt test, measurement of supine plasma noradrenaline (norepinephrine, NA), measurement of R-R variability (CV R-R), and intravenous infusions of NA and isoproterenol.

**Results**—Urinary symptoms (96%) were found to be more common than orthostatic symptoms (43%) ( $p < 0.01$ ) in patients with MSA, particularly with OPCA ( $p < 0.01$ ) and SND ( $p < 0.01$ ) types. In 53 patients with both urinary and orthostatic symptoms, patients who had urinary symptoms first (48%) were more common than those who had orthostatic symptoms first (29%), and there were patients who developed both symptoms simultaneously (23%). Post-micturition residuals were noted in 74% of the patients. EMG cystometry showed detrusor hyperreflexia in 56%, low compliance in 31%, atonic curve in 5%, detrusor-sphincter dyssynergia in 45%, and neurogenic sphincter EMG in 74%. The cystometric curve tended to change from hyperreflexia to low compliance, then atonic curve in repeated tests. Bethanechol injection showed denervation supersensitivity of the bladder in 19%. Cardiovascular tests showed orthostatic hypotension below  $-30$  mm Hg in 41%, low CV R-R below 1.5 in 57%, supine plasma NA below 100 pg/ml in 28%, and denervation supersensitivity of the vessels ( $\alpha$  in 73%;  $\beta_2$  in 60%) and of the heart ( $\beta_1$  in 62%).

**Conclusion**—It is likely that urinary dysfunction is more common and often an earlier manifestation than orthostatic hy-

**potension in patients with MSA, although subclinical cardiovascular abnormalities appear in the early stage of the disease. The responsible sites seem to be central and peripheral for both dysfunctions.**

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**Keywords:** autonomic dysfunction; multiple system atrophy; orthostatic hypotension; urinary incontinence; urodynamic study

Multiple system atrophy (MSA)<sup>c</sup> is known to have urinary disturbance.<sup>1,2</sup> Some male patients with MSA have undergone urological surgery for prostatic hypertrophy before the correct diagnosis had been made. The results of the surgery are often transient or unfavourable because of the progressive nature of this disease. Previously we investigated urinary function in 86 patients with MSA considering three clinical variants; striatonigral degeneration (SND), sporadic olivopontocerebellar atrophy (OPCA), and the Shy-Drager syndrome.<sup>3</sup> The study showed that 4% of the patients with OPCA type, 16% with SND type, and 50% with Shy-Drager type had urinary symptoms at the onset of disease, and in particular 17% of the patients with Shy-Drager type had urinary symptoms as the sole initial symptom. Orthostatic hypotension was pointed out first in patients with Shy-Drager type,<sup>4</sup> which turned out to be a marker of autonomic involvement in MSA.<sup>5,6</sup> Both of the original two patients had urinary frequency, incontinence, and urinary retention as well.<sup>4</sup> The other two variants rarely develop orthostatic hypotension in their early stage; however, both the patients with OPCA type had voiding difficulty and urinary incontinence,<sup>7</sup> and three of four with SND type showed voiding difficulty, retention, and urinary incontinence.<sup>8</sup> In this paper we present data from a detailed questionnaire and autonomic function tests in 121 patients with MSA concerning both urinary and cardiovascular systems.

## Patients and methods

### PATIENTS AND AUTONOMIC QUESTIONNAIRE

The autonomic questionnaire comprised urinary symptoms including nocturnal and diurnal urinary frequency, sensation of urgency, urinary incontinence, voiding difficulty and retention, and orthostatic symptoms including postural faintness, blurred vision, and syncope. We gave the questionnaire to 121 patients with a clinical diagnosis of MSA,<sup>9,10</sup> including 74

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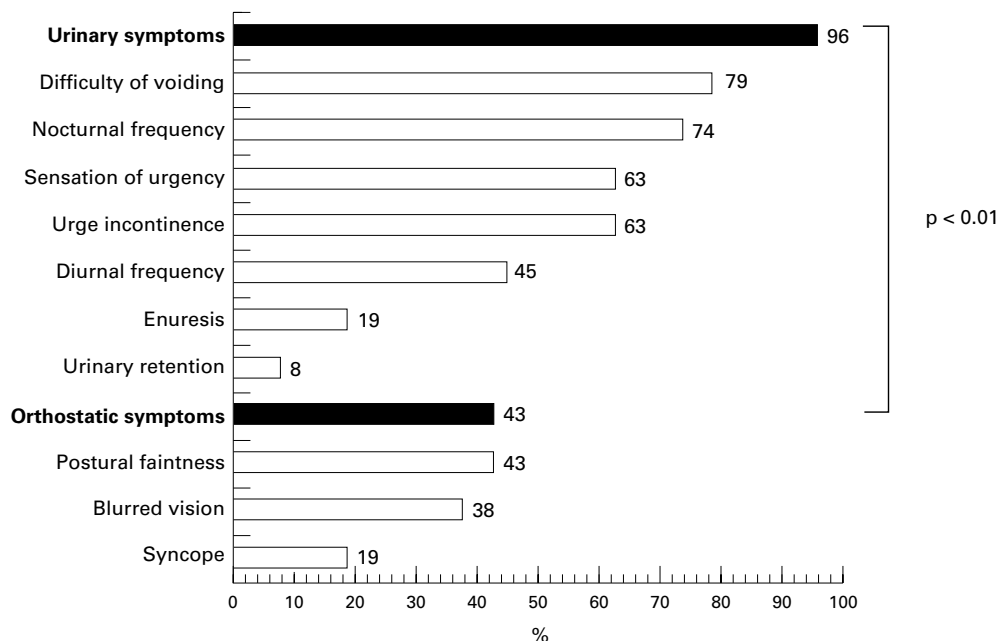


Figure 1 Urinary and orthostatic symptoms in patients with MSA.

men and 47 women, mean age 58 (SD 8.0) years). We also divided the patients into three variants; OPCA type in 48, SND type in 17, and Shy-Drager type in 56. In the OPCA type, cerebellar ataxia is the initial and main clinical feature that may be gradually overlapped by parkinsonism during the course of disease. In the SND type, parkinsonism is the initial and main clinical feature throughout the course of the disease. In the Shy-Drager type, autonomic symptoms are the initial and main clinical feature and mild parkinsonism, cerebellar ataxia, and/or pyramidal involvement appear during the course of the disease in all patients, which enables the exclusion of pure autonomic failure.<sup>5,6</sup> The duration of the disease was 1–2 years in 44, 3–4 years in 39, and over 5 years in 38. None had abnormalities on ECG or chest radiography, and in blood chemistry (including blood sugar), urinalysis, or abdominal ultrasonography (including kidney and prostate). The normal ranges of the cardiovascular function tests were obtained from 11 neurologically

normal control subjects aged 55 (SD 9.9) years<sup>11</sup> and the previous reports.<sup>12,13</sup>

#### URODYNAMIC STUDIES AND CARDIOVASCULAR TESTS

After voluntary voiding we measured post-micturition residuals, and their normal volume is under 30 ml. The EMG cystometry, medium fill (50 ml/min) water cystometry with simultaneous sphincter EMG was done with a electromyographic computer (Nihon Kohden; Neuropack Σ) and a urodynamic computer (Lifetech; Janus). The filling phase abnormalities included detrusor hyperreflexia which is a phasic contraction with a detrusor pressure rise ( $\Delta P_{det}$ ) over 10 cm H<sub>2</sub>O, and low compliance bladder which is a tonic contraction of the detrusor with bladder capacity / $\Delta P_{det}$  under 20 ml/cm H<sub>2</sub>O. An atonic curve is defined when the patient has a bladder capacity over 600 ml and is unable to contract the detrusor on voiding. Detrusor-sphincter dyssynergia is defined when the patient is unable to relax the sphincter on voiding. The methods and definitions used for the urodynamic studies conformed to the standards proposed by the International Continence Society.<sup>14</sup> Seventeen of the patients had repeated urodynamic studies. Analysis of sphincter EMG was performed in 70 patients. Neurogenic sphincter EMG is defined as long duration over 10 ms, polyphase more than five phases, and high amplitude over 600  $\mu$ V. A bethanechol test was performed in 53 patients. After infusion of 100 ml water, 2.5 mg bethanechol chloride was injected subcutaneously and detrusor pressure was measured for 30 minutes.  $\Delta P_{det}$  over 15 mm H<sub>2</sub>O during the test is considered to be high.<sup>15</sup>

The head up tilt test (80 degrees, 10 minutes) was carried out while monitoring blood pressure (BP) and heart rate (HR) with an automatic sphygmomanometer (Nihon

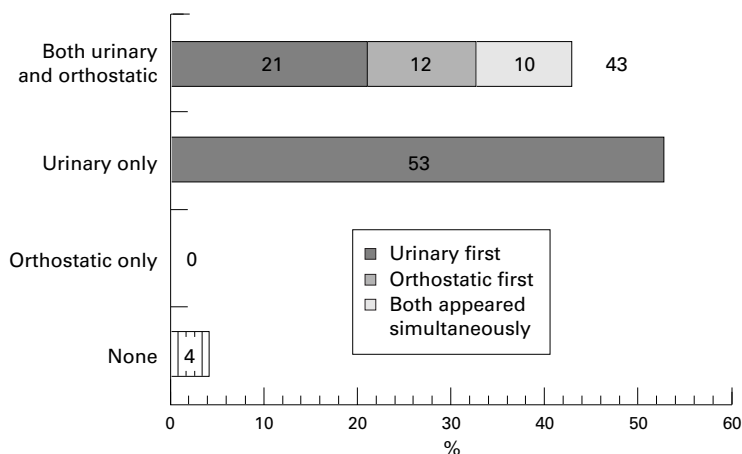


Figure 2 Timing of urinary and orthostatic symptoms in patients with MSA.

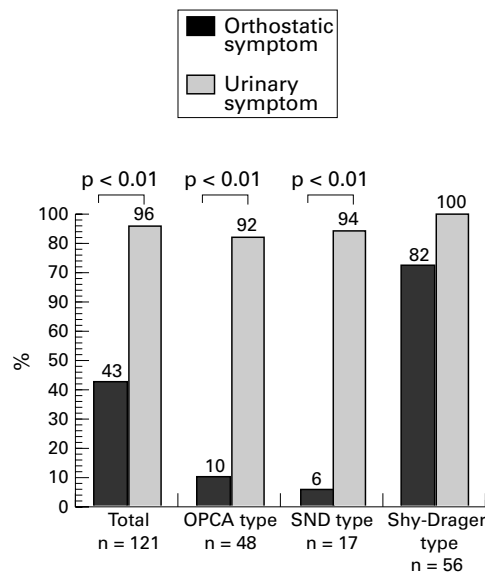


Figure 3 Urinary and orthostatic symptoms in three variants of MSA.

Kohlin; BP-203Y). Systolic blood pressure fall ( $\Delta$ BPsys) was  $-0.2$  (SD 10.7) mm Hg in the control group, and below  $-30$  mm Hg is regarded as low considering its variation with age. Supine plasma noradrenaline (norepinephrine) (NA) was measured in 88 patients. It was 188.8 (SD 80.4) pg/ml in the control group, and below 100 pg/ml is regarded as low. R-R variability (CV R-R) was measured in 98 patients by an arrhythmia computer (ME Commercial; Automatic R-100). CV R-R was 3.37 (SD 0.55) in the control group, and below 1.5 is regarded as low considering its variation with age. Infusion of NA was performed in 89 patients at a rate of 0.05 mg/kg/min for 3 min-

utes and 0.1 mg/kg/min. for the following 3 minutes to avoid extreme hypertension.  $\Delta$ BPsys during the infusion was 10.4 (SD 6.2) mm Hg in the control group, and over 30 mm Hg is considered to be high. Isoproterenol infusion was performed in 85 patients at a rate of 0.02 mg/kg/min for 5 minutes. Change in heart rate ( $\Delta$ HR) during the infusion was 38.8 (SD 11)/min in the control group, and over 50/min is considered to be high.  $\Delta$ BPsys during the infusion was  $-6.7$  (SD 9.8) mm Hg in the control group, and below  $-20$  mm Hg is considered to be low.

**Results**

The autonomic questionnaire showed that 96% of the patients had urinary symptoms (figures 1 and 2). The most frequent symptom was difficulty of voiding in 79%, followed by nocturnal urinary frequency in 74%, sensation of urgency in 63%, and urge incontinence in 63%, and urinary retention was noted in 8%. Orthostatic symptoms were found in 43% of the patients, including postural faintness in 43%, blurred vision in 38%, and syncope in 19%. Urinary symptoms were more common than orthostatic symptoms ( $p < 0.01$ ). In 43% of patients with both urinary and orthostatic symptoms, patients who had urinary symptoms first (21%) were more common than those who had orthostatic symptoms first (12%), although there was no statistical significance, and there were patients who developed both symptoms simultaneously (10%). Fifty three per cent of the patients had only urinary symptoms but none had only orthostatic symptoms. In three variants of MSA, the difference between urinary and orthostatic symptoms was prominent in patients with OPCA type (urinary symptoms in 92% and orthostatic symptoms in 10%;  $p < 0.01$ ) and with SND type (94% and 6%, respectively;  $p < 0.01$ ) compared with those with Shy-Drager type (100% and 82%, respectively, fig 3).

Results of urodynamic studies showed postmicturition residuals in 74% of the patients, and those over 100 ml were noted in 52% (fig 4). EMG cystometry showed detrusor hyperreflexia in 56%, low compliance bladder in 31%, atonic curve in 5%, detrusor-sphincter dyssynergia in 45%, and neurogenic change in 74% of the patients. Bethanechol injection showed  $\Delta$ Pdet over 15 mm H<sub>2</sub>O in 19% of the patients. Repeated urodynamic studies of 17 patients showed cystometric findings changing from hyperreflexia to low compliance bladder in eight patients (after 2-3 years), and then one of them developed an atonic curve. The cystometric curve also changed from normal to low compliance bladder in three (after 2 years). Two patients initially with a negative bethanechol test developed denervation supersensitivity (after 2-3 years). Sphincter EMG changed from normal to detrusor-sphincter dyssynergia in five patients (after 2-4 years), and from normal to neurogenic in two (after 2 years). Results of cardiovascular tests showed orthostatic hypotension below  $-30$  mm Hg in 41%, low CV R-R below 1.5 in 57%, and supine plasma NA below 100 pg/ml in 28% of the

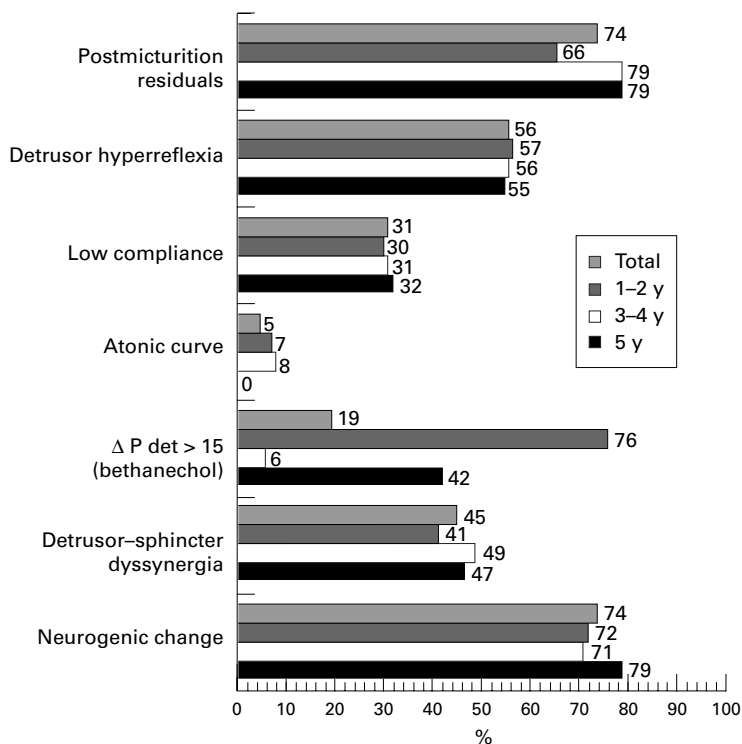


Figure 4 Results of urodynamic studies in patients with MSA.

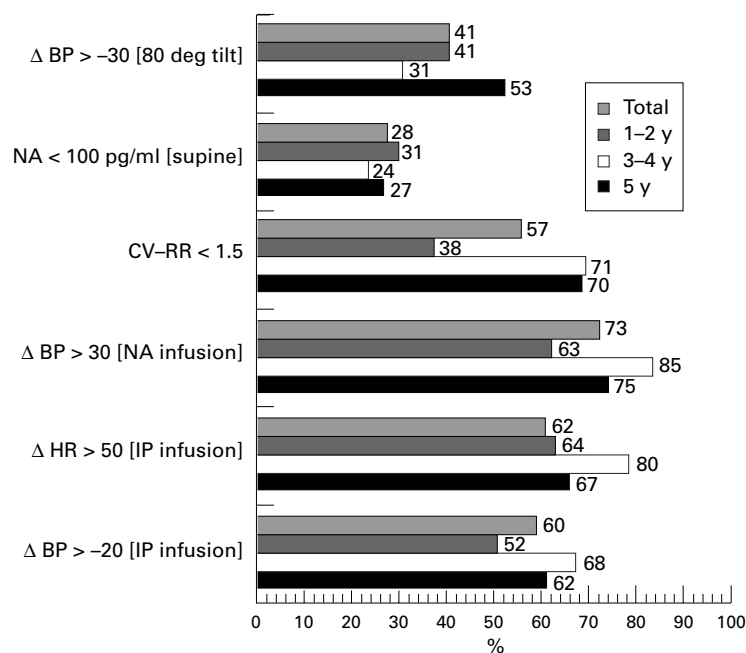


Figure 5 Results of cardiovascular tests in patients with MSA.

patients (fig 5). Infusion of NA showed  $\Delta$  BPsys over 30 mm Hg in 73% of the patients. Isoproterenol infusion showed  $\Delta$ HR over 50/min. in 62%, and a  $\Delta$  BPsys fall below -20 mm Hg in 60% of the patients. These abnormalities were noted even in the early stages of the disease.

### Discussion

The analysis of the detailed questionnaire and autonomic function tests in this series of 121 patients with clinically diagnosed MSA, is the first of its kind concerning both urinary and cardiovascular systems. Urinary dysfunction has attracted less attention than postural hypotension in patients with MSA. The results of the present study, however, showed that urinary symptoms (96%) were more common than orthostatic symptoms (43%) ( $p < 0.01$ ). The most frequent urinary symptom was difficulty of voiding, in 79% of our patients, followed by nocturnal urinary frequency in 74%, and the other symptoms were sensation of urgency in 63%, urge incontinence in 63%, diurnal urinary frequency in 45%, enuresis in 19%, and urinary retention in 8%. The most frequent orthostatic symptom was postural faintness in 43%, followed by blurred vision in 38% and syncope in 19%. Previously Wenning *et al*<sup>6</sup> mentioned urinary incontinence in 71% and urinary retention in 27%, and postural faintness in 53% and syncope in 15% of their 100 clinically diagnosed cases. In our 53 patients with both urinary and orthostatic symptoms, patients who had urinary symptoms first (48%) were more common than those who had orthostatic symptoms first (29%), although this difference was not significant, and there were patients who developed both symptoms simultaneously (23%). These results indicate that urinary dysfunction is more common and often an earlier manifestation than

orthostatic hypotension in MSA. We also divided MSA patients into three variants, showing that the difference between urinary and orthostatic symptoms is prominent in patients with OPCA type (urinary symptoms in 92% and orthostatic symptoms in 10%;  $p < 0.01$ ) and with SND type (94% and 6%, respectively;  $p < 0.01$ ) compared with those with Shy-Drager type (100% and 82%, respectively).

The results of urodynamic studies showed postmicturition residuals in 74% of our patients, and residuals over 100 ml were noted in 52%. EMG cystometry showed detrusor hyperreflexia in 56%, low compliance bladder in 31%, atonic curve in 5%, detrusor-sphincter dyssynergia in 45%, and neurogenic sphincter EMG in 74% of the patients. Bethanechol injection showed  $\Delta$ Pdet over 15 mm H<sub>2</sub>O suggestive of denervation supersensitivity of the bladder,<sup>15</sup> in 19% of the patients. These findings indicate the presence of central and peripheral types of urinary dysfunction in MSA. The results seem to be relevant to the pathological lesions reported in MSA,<sup>17</sup> which include the locus ceruleus (pontine micturition centre),<sup>18,19</sup> the putamen, the substantia nigra,<sup>20</sup> sacral intermediolateral nucleus,<sup>21,22</sup> and Onuf nucleus,<sup>1,23</sup> and, less contributory, the frontal cortex<sup>24-26</sup> and postganglionic cholinergic fibres.<sup>17</sup> Cardiovascular function tests showed postural hypotension below -30 mm Hg in 41%, low CV R-R below 1.5 in 57%, and supine plasma NA below 100 pg/ml in 28%. Infusion of NA showed  $\Delta$  BPsys over 30 mm Hg suggesting  $\alpha$  supersensitivity of the vessels in 73% of the patients. Isoproterenol infusion gave a  $\Delta$ HR over 50/min. suggesting  $\beta$ 1 supersensitivity of the heart in 62%, and a  $\Delta$  BPsys fall below -20 mm Hg suggesting  $\beta$ 2 supersensitivity of the vessels in 60% of the patients. These findings indicate the presence of postganglionic type cardiovascular dysfunction, and a central type of dysfunction is reported to occur in MSA.<sup>5,6</sup> These results seem to be relevant to the pathological lesions reported in MSA,<sup>17,27,28</sup> which include the medullary cardiovascular centre (the solitary tract nucleus, the area reticularis superficialis ventrolateralis, the arcuate nucleus, and the dorsal vagal motor nuclei),<sup>29,30</sup> intermediolateral cell columns of the thoracic cord, sympathetic ganglia<sup>31</sup> and postganglionic adrenergic fibres.<sup>32</sup>

In conclusion, we found that urinary dysfunction is more common and often an earlier manifestation than orthostatic hypotension in MSA, although subclinical cardiovascular abnormalities appear in the early stage of the disease. The responsible sites seem to be central and peripheral for both dysfunctions.

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