Assessment of autonomic dysfunction of multiple system atrophy with laryngeal abductor paralysis as an early manifestation

Kazushi Deguchi a,*, Kazuyo Ikeda a, Mieko Shimamura a, Yoshiteru Urai a, Masago Tsukaguchi a, Tetsuo Touge b, Hiroaki Takeuchi c, Iwao Sasaki d, Shigeki Kuriyama a

a Department of Gastroenterology and Neurology, Kagawa University School of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan
b Department of Health Sciences, Kagawa University School of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan
c Kaisei Hospital, 3-5-28 Marunouchi, Sakaide-shi, Kagawa 762-0007, Japan
d Department of Neurology, Kagawa Inoshita Hospital, 818-1 Hanaino, Onohara-cho, Kan-onji-shi, Kagawa 769-1613, Japan

Received 2 April 2007; received in revised form 14 June 2007; accepted 25 July 2007

Abstract

Laryngeal abductor palsy (LAP) is common in the advanced stages of multiple system atrophy (MSA). However, occurrence of LAP in the early stages might make a diagnosis of MSA difficult. To search for a clue to diagnosis of MSA with LAP as an early manifestation, we assessed the clinical features of autonomic dysfunction and the central cardiovascular control circuits in two MSA patients who had LAP as a cardinal symptom in the early stages. Development of autonomic dysfunction was preceded or followed by LAP. The autonomic symptom occurring predominantly in the earliest stages was urinary disturbance rather than orthostatic hypotension. Although screening cardiovascular autonomic function tests did not conclusively indicate a diagnosis of MSA, vasopressin release in response to head-up tilt and growth hormone response to clonidine administration demonstrated inappropriate responses, suggesting that the noradrenergic neurons of the caudal ventrolateral medulla were impaired. Diagnosis of atypical MSA with LAP in the early stages might be accelerated by a detailed investigation focused on urinary symptoms and neuroendocrine approaches.

Keywords: Autonomic failure; Multiple system atrophy; Laryngeal abductor paralysis; Stridor; Urinary dysfunction; Vasopressin; Growth hormone

1. Introduction

It has been well recognized that laryngeal abductor palsy (LAP) and nocturnal laryngeal stridor are among the “red flags” which may raise suspicion of multiple system atrophy (MSA) [1]. Although these symptoms are certainly common in the advanced stages, LAP as an early manifestation has been demonstrated only in 4% of patients with probable MSA [2]. In this case, an accurate early diagnosis is often difficult, and long-term follow-up may be required to make a final diagnosis of MSA.

Since impairment of the autonomic nervous system is critical for a diagnosis of MSA [3], an investigation focused on clinical and laboratory autonomic findings might provide an important clue to the early diagnosis of such atypical patients. In MSA patients with a conventional clinical course, urinary dysfunction is a more common and often an earlier manifestation than orthostatic hypotension (OH) [4]. In addition, it has been suggested that impairment of the noradrenergic (A1) neurons of the caudal ventrolateral medulla (VLM) involved in vasopressin (AVP) release in response to head-up tilt (HUT) and growth hormone (GH) response to clonidine may predominantly occur in the early stages of MSA [5]. However, since most patients presenting with LAP have been initially examined by an otorhinolaryngologist, it remains unknown whether or not patients...
presenting with LAP have clinical and/or laboratory findings similar to the conventional MSA at the first medical examination.

We presented here two cases of MSA with LAP as an early manifestation. The aim of this study was to clarify a valuable marker for early diagnosis of the atypical form of MSA. It was for that purpose that we assessed clinical features of autonomic dysfunction and the central cardiovascular control circuits in the atypical MSA patients in whom LAP was a cardinal symptom in the early stages.

2. Case reports

2.1. Case 1

A 54-year-old man was well until the age of 48, when he became aware of difficulty breathing during infection with a cold. Five years later, he visited an otorhinolaryngologist complaining of exertional dyspnea. A diagnosis of LAP was made and a laser incision of the vocal cord was performed. In addition, development of obstructive sleep apnea was confirmed by a polysomnograph. Six months later, he was referred to our outpatient clinic because of unsteady gait. Neurological examination showed extremely mild cerebellar ataxia (gait ataxia and limb ataxia), difficulty of voiding (a small amount of residual urine) and impotence. Hoarse voice was also observed. Extensor plantar responses with hyperreflexia occurred. Brain MRI showed no abnormality except a suspected atrophy of the cerebellar vermis.

Cardiovascular autonomic function tests revealed normal blood pressure (BP) responses during postural challenge (60° HUT and active standing), handgrip and cold immersion. Heart rate (HR) responses to deep breathing and Valsalva maneuver were also normal (Table 1). Phase IV BP during Valsalva maneuver showed normal BP “overshoots”. Post-prandial hypotension was not observed following 75 g glucose ingestion. Plasma noradrenaline (NA) levels at supine rest and ΔNA upon 60° HUT were normal (Table 1). Although mean BP upon 60° HUT showed little change (2% increment), an obvious decrease in the plasma concentration of AVP (−2.2 pg/ml) was observed. The abnormal AVP response was less than the lower limit of the 99% confidence bands for mean of healthy controls [5]. A clonidine-GH test was carried out by oral administration, but not by the now accepted protocol for intravenous administration [6] because clonidine injection has not been available for medical examination in Japan. To be brief, clonidine was given orally at a dose of 0.15 mg. Blood for measuring GH was sampled 30 min after administration of clonidine and every 30 min thereafter up to 3 h [7]. The increases in GH (ΔGH) and the areas under curve (AUC) following oral clonidine administration were only slight, which was equivalent to the response in MSA (Table 2).

---

**Table 1**

Results of cardiovascular autonomic function

<table>
<thead>
<tr>
<th>Test</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Probable MSA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-up tilt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Systolic (mmHg)</td>
<td>4</td>
<td>−72</td>
<td>−40 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Δ Diastolic (mmHg)</td>
<td>1</td>
<td>−42</td>
<td>−20 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Systolic (mmHg)</td>
<td>18</td>
<td>−76</td>
<td>−41 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Δ Diastolic (mmHg)</td>
<td>16</td>
<td>−47</td>
<td>−24 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Isomeric hand grip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Systolic (mmHg)</td>
<td>2</td>
<td>1</td>
<td>2 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Δ Diastolic (mmHg)</td>
<td>5</td>
<td>2</td>
<td>−1 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Mental arithmetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Systolic (mmHg)</td>
<td>−3</td>
<td>−24</td>
<td>3 (3)</td>
<td>21 (3)</td>
</tr>
<tr>
<td>Δ Diastolic (mmHg)</td>
<td>−4</td>
<td>−10</td>
<td>−4 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Cutaneous cold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Systolic (mmHg)</td>
<td>20</td>
<td>17</td>
<td>9 (4)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>Δ Diastolic (mmHg)</td>
<td>21</td>
<td>4</td>
<td>1 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Deep breathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Heart rate (beats/min)</td>
<td>14</td>
<td>4</td>
<td>7 (2)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Valsalva</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio</td>
<td>1.37</td>
<td>1.09</td>
<td>1.22 (0.02)</td>
<td>1.43 (0.04)</td>
</tr>
<tr>
<td>Plasma NA at rest and in response to HUT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA at rest (pg/ml)</td>
<td>389</td>
<td>46</td>
<td>114 (11)</td>
<td>247 (30)</td>
</tr>
<tr>
<td>ΔNA (pg/ml)</td>
<td>119</td>
<td>33</td>
<td>76 (15)</td>
<td>142 (15)</td>
</tr>
</tbody>
</table>

MSA: multiple system atrophy; NA: noradrenaline; HUT: head-up tilt.

* Data from autonomic function tests in 14 probable MSA patients (63 ± 3 years old) and 24 healthy subjects (63 ± 3 years old). Values are the means (S.E.).
2.1. Case 1

A 71-year-old woman was well until the age of 67, when she had urinary incontinence. About 30 months after the onset of incontinence, she lost consciousness for the first time when getting out of a car. After this initial incident, she experienced syncope on standing several times. Four months later, increased snoring and apnea were noticed by her daughter. She visited her family doctor, where it was pointed out that her frequent syncope might be attributable to her severe OH (180/80 mmHg to 50/30 mmHg). In addition, a polysomnograph demonstrated the involvement of obstructive sleep apnea, and a diagnosis of LAP was made by an otorhinolaryngologist. She was referred to our outpatient clinic because of a detailed examination of the causes of OH. Neurological examination showed normal findings except autonomic dysfunction. Brain MRI showed no abnormality except a slight ischemic change of the white matter. \(^{[123]}\)I Metaiodobenzylguanidine (MIBG) myocardial scintigraphy demonstrated normal myocardial uptake of MIBG.

Cardiovascular autonomic function tests revealed OH upon postural challenge, decreased pressor responses to isometric exercise and mental arithmetic and decreased HR responses to deep breathing and the Valsalva maneuver (Table 1). There were no BP “overshoots” during phase IV of the Valsalva maneuver. Plasma NA levels at rest and \(\Delta NA\) upon 60° HUT were extremely low (Table 1). Although a 52% decline in mean BP upon 60° HUT was observed, \(\Delta AVP\) showed an insufficient response (0.8 pg/ml), which corresponded to the lower limit of the 99% confidence band for the mean of the healthy controls \(^{[5]}\). The values of \(\Delta GH\) and AUC were low following oral clonidine (0.15 mg) administration, which was equivalent to the response in MSA (Table 2).

Several months after these investigations, the patient died suddenly during sleep. An autopsy was not permitted by her family.

### Table 2

<table>
<thead>
<tr>
<th>Serum GH increment and AUC to oral clonidine</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Probable MSA</th>
<th>PD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta GH) (ng/ml)</td>
<td>3.4</td>
<td>2.7</td>
<td>2.3 (0.9)</td>
<td>11.6 (2.6)</td>
</tr>
<tr>
<td>AUC</td>
<td>316.5</td>
<td>313.5</td>
<td>257.4 (65.5)</td>
<td>1097.0 (148.7)</td>
</tr>
</tbody>
</table>

GH: growth hormone; AUC: area under the curve; MSA: multiple system atrophy; PD: Parkinson’s disease.

* Data from oral clonidine test in 14 probable MSA patients (63 ± 3 years old) and 3 PD patients (66 ± 8 years old). Values are the means (S.E.).

2.2. Case 2

A 71-year-old woman was well until the age of 67, when she had urinary incontinence. About 30 months after the onset of incontinence, she lost consciousness for the first time when getting out of a car. After this initial incident, she experienced syncope on standing several times. Four months later, increased snoring and apnea were noticed by her daughter. She visited her family doctor, where it was pointed out that her frequent syncope might be attributable to her severe OH (180/80 mmHg to 50/30 mmHg). In addition, a polysomnograph demonstrated the involvement of obstructive sleep apnea, and a diagnosis of LAP was made by an otorhinolaryngologist. She was referred to our outpatient clinic because of a detailed examination of the causes of OH. Neurological examination showed normal findings except autonomic dysfunction. Brain MRI showed no abnormality except a slight ischemic change of the white matter. \(^{[123]}\)I Metaiodobenzylguanidine (MIBG) myocardial scintigraphy demonstrated normal myocardial uptake of MIBG.

Cardiovascular autonomic function tests revealed OH upon postural challenge, decreased pressor responses to isometric exercise and mental arithmetic and decreased HR responses to deep breathing and the Valsalva maneuver (Table 1). There were no BP “overshoots” during phase IV of the Valsalva maneuver. Plasma NA levels at rest and \(\Delta NA\) upon 60° HUT were extremely low (Table 1). Although a 52% decline in mean BP upon 60° HUT was observed, \(\Delta AVP\) showed an insufficient response (0.8 pg/ml), which corresponded to the lower limit of the 99% confidence band for the mean of the healthy controls \(^{[5]}\). The values of \(\Delta GH\) and AUC were low following oral clonidine (0.15 mg) administration, which was equivalent to the response in MSA (Table 2).

Several months after these investigations, the patient died suddenly during sleep. An autopsy was not permitted by her family.

### 3. Discussion

Patient 1 developed LAP followed by residual urine accompanied by erectile dysfunction and cerebellar ataxia. On the other hand, Patient 2 initially showed urinary incontinence and then frequent syncope due to OH. Soon after that, LAP and obstructive sleep apnea were confirmed. Previous reports have also demonstrated a characteristic clinical course of either autonomic dysfunction preceded by LAP or autonomic dysfunction followed by LAP. The former was reported to take a few years (up to 6 years) until development of autonomic symptoms \(^{[8–13]}\), and the latter from 2 months to a few years (up to 6 years) until diagnosis of LAP \(^{[11,14–18]}\). Thus, the clinical course of atypical cases with outstanding LAP in the early stages might be classified into two types.

Although urinary dysfunction has attracted less attention than OH in patients with MSA, it has been shown that urinary dysfunction predominantly occurs in the early stages of MSA \(^{[4]}\). The most frequent urinary symptom is difficulty of voiding, followed in order by nocturnal urinary frequency, sensation of urgency, urge incontinence, diurnal urinary frequency, enuresis and urinary retention \(^{[4]}\). Such urinary symptoms have been mentioned quite often as the earliest autonomic manifestations in atypical MSA patients showing LAP initially, as in the present cases \(^{[8,9,11,13,14,16,18]}\). Therefore, it is certain that urinary symptoms could be a valuable clue for early diagnosis even in atypical cases with LAP in the early stages as well as conventional MSA.

Autonomic screening tests near the time of LAP onset demonstrated severe sympathetic and parasympathetic failure in Patient 2 with LAP preceded by autonomic dysfunction. In addition, this patient had a substantially low basal level of NA, suggesting postganglionic sympathetic impairment. Since she had not developed the clinical domains (parkinsonism and cerebellar dysfunction) required for diagnosis of MSA \(^{[3]}\), discrimination of pure autonomic failure (PAF) with sleep apnea syndrome \(^{[19]}\) might be a diagnostic issue. However, the neuroendocrine approaches, namely insufficient responses of AVP during HUT \(^{[5]}\) and GH following clonidine \(^{[6]}\), were in favor of a diagnosis of MSA where the lesion site is preganglionic, but not of PAF where the lesion site is postganglionic. Although few oral clonidine-GH tests have been used in the investigation of parkinsonian syndromes, the validity of this method could be supported for the following reasons: (1) oral clonidine as well as intravenous clonidine produced a satisfactory GH response (GH increment \(\geq 4\) ng/ml from basal, 90 min after clonidine) in healthy adults \(^{[20]}\); (2) GH responses to oral clonidine in patients with MSA and Parkinson’s disease \(^{[7]}\) were equivalent to previous reports using intravenous clonidine \(^{[6]}\). In addition, normal myocardial uptake of MIBG was consistent with the diagnosis of MSA, but not of PAF \(^{[21]}\).

In Patient 1 with LAP followed by autonomic dysfunction, OH was absent and urinary dysfunction was minimal even 6
years after the onset of LAP. Under these circumstances, he was diagnosed as MSA tentatively based on the insufficient responses of AVP during HUT [5] and GH following clonidine [6], as in Patient 2. During follow-up of the clinical course, the diagnosis of MSA was confirmed clinically by development of parkinsonism and exacerbation of cerebellar ataxia and urinary dysfunction. The process of diagnosis in Patients 1 and 2 suggests that the use of autonomic screening tests alone was not sufficient for an accurate diagnosis of the atypical cases with LAP in the early stages.

Depletion of catecholamine neurons in the rostral VLM projecting to the sympathetic preganglionic neurons and the caudal VLM projecting to the hypothalamus has been demonstrated in patients with MSA [22]. Of these central cardiovascular control circuits, predominant impairment of the A1 neurons of the caudal VLM in the early stages of MSA has been suggested by the lack of AVP increase and intact NA release in response to HUT [5]. Since loss of the A1 neurons could be followed by denervation of the hypothalamus [22], an impaired GH response to the α2-agonist clonidine also might be expected in the early stages of MSA. Although reduced responses to a clonidine test have not been demonstrated in the early stages of patients with conventional MSA, inadequate responses of GH to the clonidine as well as inadequate AVP release upon HUT were observed in Patients 1 and 2 in the present work. These findings suggest that impairment of the central cardiovascular control circuits in MSA with LAP as an early manifestation could be equivalent to that in MSA with a conventional clinical course. Therefore, these neuroendocrine approaches might be valuable for early diagnosis of MSA regardless of the clinical phenotype.

In conclusion, the clinical course of MSA with LAP as an early manifestation might be classified into two types—namely, autonomic dysfunction preceded by LAP and autonomic dysfunction followed by LAP. In both clinical types, urinary dysfunction very frequently occurs. Although screening cardiovascular autonomic function tests were of no significance, the AVP release upon HUT and GH response to clonidine administration demonstrated inadequate responses reflecting impairment of the central cardiovascular control circuits. Therefore, investigations of urinary conditions by a questionnaire or urodynamic studies and neuroendocrine approaches by AVP and GH responses might provide a valuable clue for early diagnosis of the atypical form of MSA.

References