Clinical Characteristics of Patients with Multiple System Atrophy in Singapore

RDG Jamora,1 MD, A Gupta,1 MRCP (UK), AKY Tan,1 MRCP (UK), FAMS, LCS Tan,1 FRCP (Edin), FAMS

Abstract

Introduction: Our study aimed to describe the clinical features of multiple system atrophy (MSA) in Singapore and verify its diagnosis using the consensus statement in the diagnosis of MSA. Materials and Methods: All patients suspected to have MSA between 1995 and March 2005 were identified from the Movement Disorders database and the autonomic function testing results. The medical records were reviewed using a standardised data collection form. The diagnosis of MSA was verified using the consensus statement. Disease progression was evaluated using 2 pre-determined events: aid-requiring walking and wheelchair use. Results: Seventy-two per cent (33/46) fulfilled the consensus statement. There were 85% Chinese, 9% Malays, and 6% Indians. The mean age at onset of the disease was 60 ± 10 years. We found a predominance of males (M:F = 1.5:1) as well as MSA-C cases (67%). The most common initial presenting features were parkinsonism and cerebellar signs (27% each). Abnormal neuroimaging was seen in 29 patients (91%). Autonomic function testing was abnormal in 58% (7/12). The risk for aid-requiring walking and wheelchair use at 3 years from onset of the disease was 31% and 17%, respectively. By 5 years, this had increased to 45% and 30%, respectively. There was no difference in the events rate between MSA subtypes. Conclusions: The clinical characteristics of MSA in Singapore are presented. Our study revealed a predominance of MSA-C patients as well as a later age at onset of disease and longer median time to aid-requiring walking and wheelchair use compared to Japanese patients.

Ann Acad Med Singapore 2005;34:553-7

Key words: Autonomic dysfunction, Cerebellar diseases, Orthostatic hypotension, Parkinsonism, Urinary incontinence

Introduction

Multiple system atrophy (MSA), a term introduced in 1969, is a progressive neurodegenerative disease which occurs sporadically and is characterised by parkinsonism, cerebellar dysfunction, and autonomic insufficiency in various combinations.1-3 It usually begins in the fifth decade and affects both sexes. MSA now includes the disorders previously called Shy-Drager syndrome, olivoponto-cerebellar atrophy (OPCA), and striatonigral degeneration (SND). The discovery of glial cytoplasmic inclusions (GCI) in the brain of patients with these conditions confirmed that SND, OPCA, and Shy-Drager syndrome are the same disease with different clinical expressions.4 Several diagnostic criteria have been proposed but no consistent guidelines have been developed.2,5,6 A consensus conference was held in 1998 and a new diagnostic criteria was adapted.5 It was then recommended that patients be designated as having MSA-C if cerebellar features predominate and MSA-P if parkinsonian features predominate, instead of using the old terms SND and sporadic OPCA, respectively.3 The term Shy-Drager syndrome was found to be no longer useful since autonomic failure is invariably present.

While the data from the west were conflicting (some reported a predominance of MSA-P5,7,8 and others reported a predominance of MSA-C9,10), a predominance of MSA-C cases was reported in Japan.11 The clinical features of MSA using the current consensus statement on the diagnosis of MSA have not been evaluated in Southeast Asia.

1 Department of Neurology
National Neuroscience Institute (TTSH Campus), Singapore
Address for Reprints: Dr Louis CS Tan, Department of Neurology, National Neuroscience Institute-TTSH Campus, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: louis_tan@nni.com.sg

This paper has been selected for inclusion in the Academy of Medicine’s Continuing Professional Development Distance-Learning Programme. Members will be able to access this article via a secured Login. More details will be available on the Academy’s website http://www.ams.edu.sg/ closer to the launch date.
Asia, an ethnically and linguistically diverse region with a population of 443 million. We therefore investigated the clinical spectrum and characteristics of MSA in Singapore, a multi-ethnic Southeast Asian country with a population of 4 million people comprising 76% Chinese, 14% Malays, and 8% Indians.

Materials and Methods

All patients identified and managed as MSA sufferers between 1995 and March 2005 at the Movement Disorders (MD) Clinic of the Department of Neurology, Tan Tock Seng Hospital (TTSH), which in 1999 became part of the new National Neuroscience Institute (NNI). The TTSH/NNI provides tertiary care to patients with neurological disorders in Singapore. An MD specialist (AKYT) started the MD database and service at TTSH in 1995. From 1995 to 2001, a single MD specialist ran a weekly MD clinic. Since then, this has increased to 3 MD clinics run weekly by 3 MD specialists. The autonomic function test results from the Neurodiagnostic Laboratory were also reviewed and all non-diabetic patients with documented postural hypotension, abnormal results, or a diagnosis of MSA were included.

Based on symptoms and/or diagnoses identified from both sources (MD database and autonomic function test results), patients suspected to have MSA were identified. Their available medical records were then retrospectively reviewed by an MD fellow (RDGJ) to obtain demographic and clinical characteristics using a standardised data collection form to verify the diagnosis of MSA using the consensus statement on the diagnosis of MSA. The progression of the disease was evaluated using 2 predetermined events: aid-requiring walking and wheelchair use. Aid-requiring walking was defined as the use at all times of a walking aid (stick, quad-cane, etc) or holding onto someone or something (a companion’s arm, wall, furniture, etc) for support. Wheelchair use was defined as the time the patient started using a wheelchair as noted by the physician in the medical records. We treated the onset of aid-requiring walking or wheelchair-bound state as the “failure” event with the time to event measured in months from the time of onset of first symptom attributable to MSA.

Quantitative variables were expressed as means ± standard deviations (SDs) while qualitative variables were expressed as percentages. The χ² test was used to compare qualitative variables and the Student’s t-test to compare means between groups. Survival curves were plotted using the Kaplan-Meier survival analysis for events (aid-requiring walking and wheelchair use). The log-rank test was used to compare the rate of events between MSA-P and MSA-C patients. The data were analysed using SPSS ver 11.5 (SPSS Inc., Chicago).

Results

We reviewed the medical records of 46 patients with suspected MSA who were then evaluated based on the consensus statement on the diagnosis of MSA. Thirteen patients who did not fulfill the criteria for probable or possible MSA were excluded. Thirty-one patients (94%) were identified from the MD database and 2 patients (6%) were identified from the autonomic function test results review. The majority (94%) were diagnosed and being managed by MD specialists, 1 (3%) by a neurologist, and 1 (3%) by a geriatrician.

The 33 patients included in this study all met the criteria for probable MSA, consisting of 20 males and 13 females (M:F ratio = 1.5:1) (Table 1). The mean age at onset of the first symptom was 60 ± 10 years (range, 41 to 76 years). There were more MSA-C patients (67%). Seven patients (21%) did not have any comorbidity. Of the remaining 79%, the most common comorbid conditions were hypertension (n = 13), stroke (n = 6), dyslipidaemia (n = 5) and anxiety/depression (n = 4). The racial composition of Chinese, Malays, and Indians in our study was comparable to that of the general population in Singapore (χ² = 1.49, P = 0.47).

The initial presenting clinical features of the disease were parkinsonism and cerebellar signs in 27% (9 patients each) (Fig. 1). Fifteen patients (45%) had features involving more than 1 system. None presented with pure autonomic failure initially. By the last clinical visit, 79% had parkinsonism, autonomic failure and cerebellar and pyramidal signs.

Parkinsonism was documented in all patients (Table 1). Levodopa (maximum dose achieved, range: 100 mg/day to 800 mg/day) was started in 67% of the patients. Some degree of subjective improvement was noted in 50% of MSA-P and in 25% of MSA-C patients. Selegiline (5 mg/
Cerebellar dysfunction

Parkinsonism

October 2005, Vol. 34 No. 9

brain. Three patients (9%) had normal neuroimaging findings. A total of 29 patients (91%) had abnormal neuroimaging. The reported neuroimaging abnormalities were cerebellar/vermian atrophy (29 patients), pontine atrophy (11) and “hot cross bun sign” in the pons (5). None of the patients were reported to have putaminal abnormalities. Only 12 patients (36%) underwent autonomic function testing, 7 of whom showed parasympathetic, sympathetic, or autonomic dysfunction; 2 had inconclusive results and 3 were normal. None had sphincter electromyography.

The rate of aid-requiring walking was 1.5/100 person months and for wheelchair use, the rate was 1.6/100 person months. The risk of aid-requiring walking at 3 years from the time of initial symptom onset was 31% and 17%, respectively. At 5 years, this had increased to 45% and 30% and by 10 years, to 81% and 73%, respectively (Figs. 2a and 2b). The median time to aid-requiring walking was 72 months (95% CI, 33 to 111) and for wheelchair use, 82 months (95% CI, 68 to 96). There was no statistically significant difference in the time to aid-requiring walking (72 months versus 82 months, $P = 0.97$, Fig. 2c) and in the time to wheelchair use (57 months versus 81 months, $P = 0.63$, Fig. 2d) between MSA-P and MSA-C patients.

### Discussion

We found that 72% (33/46) of our patients fulfilled the consensus statement for the diagnosis of MSA. This was slightly lower than the 80% (230/286) reported in a Japanese study, which used the same criteria. There may be some difficulty in the diagnosis of MSA partly due to the fact that 10% to 20% of MSA cases present with relatively pure parkinsonism (asymmetry, levodopa-responsiveness, development of levodopa-induced dyskinesias and motor fluctuations). While the use of the current diagnostic criteria for MSA may improve the accuracy of diagnosis at first visit, at the last visit they are no more accurate than the neurologist’s final diagnosis. The reported sensitivity of the consensus statement using neuropathologically examined cases ranges between 63% and 88%.

Our study showed a male predominance (M:F, 1.3:1), as seen in previous studies (range, 1.2 to 2.0:1). We also noted a predominance of MSA-C cases (67%) compared to MSA-P (33%), which is similar to the series from Japan.

Another difference in our study was the later mean age of onset of MSA in our patients (60 years) compared to that in published data (54.2 years to 55.4 years). Our median time from symptom onset to aid-requiring walking and wheelchair use was 2 times and 1.4 times longer respectively, when compared to Japanese patients. These differences are difficult to explain. It is tempting to speculate that our MSA patients may have a more benign course compared to

### Table 1. Comparison of Demographic and Clinical Data of MSA Patients According to MSA Subtypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSA-P n = 33</th>
<th>MSA-C n = 33</th>
<th>Total n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>20 (61)</td>
<td>12 (37)</td>
<td>32 (48)</td>
</tr>
<tr>
<td>Age at onset of MSA, years</td>
<td>60 (10)</td>
<td>58 (7)</td>
<td>118 (18)</td>
</tr>
<tr>
<td>Race</td>
<td>31 (94)</td>
<td>28 (85)</td>
<td>59 (89)</td>
</tr>
<tr>
<td>Age at diagnosis of MSA, years</td>
<td>63 (9)</td>
<td>61 (7)</td>
<td>124 (18)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>29 (88)</td>
<td>22 (66)</td>
<td>51 (77)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>27 (82)</td>
<td>16 (48)</td>
<td>43 (65)</td>
</tr>
<tr>
<td>Postural instability*</td>
<td>16 (48)</td>
<td>6 (18)</td>
<td>22 (33)</td>
</tr>
<tr>
<td>Tremor (postural, rest or both)</td>
<td>11 (33)</td>
<td>4 (12)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Autonomic and urinary dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>31 (94)</td>
<td>9 (26)</td>
<td>40 (60)</td>
</tr>
<tr>
<td>Urine specific gravity (mg/dL)</td>
<td>19 (56)</td>
<td>15 (45)</td>
<td>34 (51)</td>
</tr>
<tr>
<td>Urinary protein (mg/dL)</td>
<td>11 (32)</td>
<td>9 (26)</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Urinary specific gravity (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total urinary protein (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>20 (61)</td>
<td>12 (37)</td>
<td>32 (48)</td>
</tr>
<tr>
<td>Ataxic dysarthria</td>
<td>18 (55)</td>
<td>17 (51)</td>
<td>35 (53)</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>20 (61)</td>
<td>18 (55)</td>
<td>38 (58)</td>
</tr>
<tr>
<td>Sustained gaze-evoked nystagmus</td>
<td>18 (55)</td>
<td>17 (51)</td>
<td>35 (53)</td>
</tr>
<tr>
<td>Postural instability*</td>
<td>16 (48)</td>
<td>6 (18)</td>
<td>22 (33)</td>
</tr>
</tbody>
</table>

MSA: multiple system atrophy; MSA-C: MSA with predominant cerebellar features; MSA-P: MSA with predominant parkinsonian features

All values are either mean [standard deviation (SD)] or n (%).
Clinical Characteristics of MSA in Singapore—RDG Jamora et al

other patients. Another reason could be that these patients were seen in a movement disorders clinic of a specialised institution, where a rehabilitative service like physiotherapy was readily available. Thus, patients were able to receive advice on falls prevention and undergo gait and balance training, which may have contributed to their continued independence. A further possibility could be that our patients, in their efforts to remain independent, delayed the use of walking aids and wheelchairs. While financial constraints could be another factor causing delayed wheelchair usage in our patients, all patients needing any form of assistance would have been referred to the institution’s social worker for financial assistance.

While Japanese MSA-P patients had significantly earlier aid-requiring walking and wheelchair dependence,\(^{11}\) we found these event rates for our MSA-P and MSA-C patients to be similar. We also saw an equal number of patients presenting with pure cerebellar or parkinsonian features while other studies reported a predominance of motor disturbance.\(^{11,17}\) In terms of autonomic features, we also found a greater number of patients with urinary disturbance as compared to orthostatic hypotension, in agreement with previous studies.\(^{20,21}\)

Autonomic function testing and neuroimaging are not part of the consensus criteria but are often used to support the diagnosis of MSA and to exclude other conditions. MRI has also been found to be useful in differentiating MSA from progressive supranuclear palsy.\(^{22}\) The majority of our patients had cerebellar-pontine atrophy on neuroimaging and none were reported to have putaminal abnormalities. A hyperintense rim at the lateral edge of the dorsolateral putamen was reported in about 32% of MSA patients in one study.\(^{11}\) Nonetheless, the MRI can be normal in up to 20% of cases.\(^{23}\) While autonomic function tests have been reported to help differentiate MSA from Parkinson’s disease (PD) and idiopathic cerebellar degenerations,\(^{24}\) a recent

---

**Fig. 2.** Overall cumulative rate free from aid-requiring walking (a) and wheelchair use (b) in MSA patients from the onset of symptoms, stratified according to MSA subtype (c, \(P = 0.97\) and d, \(P = 0.63\)).
publication reported that autonomic function testing may not distinguish MSA from PD, since the clinical combination of parkinsonism and dysautonomia is as likely to be caused by PD as by MSA.25

As our study strictly adhered to the latest consensus criteria for the diagnosis of MSA, there is greater confidence in the accuracy of the diagnosis in our cases. However, missed cases can occur as a result of the early cases misdiagnosed as other types of parkinsonism. Also, not all our patients had MRI of the brain performed and the neuroimaging was not prospectively performed. As such, subtle abnormalities could have been missed by the neuroradiologists. Another limitation is the small number of our study population and that no neuropathological confirmation was available for our patients with MSA.

Despite these limitations, this is a review of the clinical characteristics of MSA patients seen in a movement disorders clinic using the consensus criteria in the diagnosis of MSA. Our study revealed a predominance of MSA-C patients as well as a later age at onset of disease and longer median time to aid-requiring walking and wheelchair use compared to Japanese patients.

Acknowledgements

We would like to thank Ms Irene Seah Soo Hoon for her assistance in this review and all the neurologists at the NNI for referring their patients to the Movement Disorders Clinic. This project was supported by the National Healthcare Group and Singapore Health Services research grants PTD/03008.

REFERENCES

2. Quinn N. Multiple system atrophy—the nature of the beast. J Neurol Neurosurg Psychiatry 1989;52(suppl):78-89.