

Progression and prognosis in multiple system atrophy

An analysis of 230 Japanese patients

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Summary

We investigated the disease progression and survival in 230 Japanese patients with multiple system atrophy (MSA; 131 men, 99 women; 208 probable MSA, 22 definite; mean age at onset, 55.4 years). Cerebellar dysfunction (multiple system atrophy–cerebellar; MSA-C) predominated in 155 patients, and parkinsonism (multiple system atrophy–parkinsonian; MSA-P) in 75. The median time from initial symptom to combined motor and autonomic dysfunction was 2 years (range 1–10). Median intervals from onset to aid-requiring walking, confinement to a wheelchair, a bedridden state and death were 3, 5, 8 and 9 years, respectively. Patients manifesting combined motor and autonomic involvement within 3 years of onset had a significantly increased risk of not only developing advanced disease stage but also shorter survival ($P < 0.01$). MSA-P patients had more rapid functional deterioration than MSA-C patients (aid-requiring walking, $P = 0.03$; confinement to a wheelchair, $P < 0.01$; bedridden state, $P < 0.01$), but showed similar survival. Onset in older individuals showed increased risk of confinement to a wheelchair ($P < 0.05$), bedridden state ($P = 0.03$) and death ($P < 0.01$). Patients initially complaining of motor symptoms had accelerated risk of aid-requiring walking ($P < 0.01$) and confinement

to a wheelchair ($P < 0.01$) compared with those initially complaining of autonomic symptoms, while the time until confinement to a bedridden state and survival were no worse. Gender was not associated with differences in worsening of function or survival. On MRI, a hyperintense rim at the lateral edge of the dorsolateral putamen was seen in 34.5% of cases, and a ‘hot cross bun’ sign in the pontine basis (PB) in 63.3%. These putaminal and pontine abnormalities became more prominent as MSA-P and MSA-C features advanced. The atrophy of the cerebellar vermis and PB showed a significant correlation particularly with the interval following the appearance of cerebellar symptoms in MSA-C ($r = 0.71$, $P < 0.01$, $r = 0.76$ and $P < 0.01$, respectively), but the relationship between atrophy and functional status was highly variable among the individuals, suggesting that other factors influenced the functional deterioration. Atrophy of the corpus callosum was seen in a subpopulation of MSA, suggesting hemispheric involvement in a subgroup of MSA patients. The present study suggested that many factors are involved in the progression of MSA but, most importantly, the interval from initial symptom to combined motor and autonomic dysfunction can predict functional deterioration and survival in MSA.

Keywords: multiple system atrophy; progression; survival; activities of daily living; early symptoms

Abbreviations: ADL = activities of daily living; CC = corpus callosum; CV = cerebellar vermis; MISS = midline internal skull surface; MPF = midline posterior fossa; MSA = multiple system atrophy; MSA-C = multiple system atrophy–cerebellar; MSA-P = multiple system atrophy–parkinsonian; OPCA = olivopontocerebellar atrophy; PB = pontine basis; SND = striatonigral degeneration

Introduction

Olivopontocerebellar atrophy (OPCA), Shy–Drager syndrome and striatonigral degeneration (SND) were described as independent clinicopathological neurodegenerative entities in 1900, 1960 and 1961, respectively (Déjerine and Thomas, 1900; Shy and Drager, 1960; Adams *et al.*, 1961). Subsequently, concurrence of OPCA with SND, and of OPCA with Shy–Drager syndrome was reported (Adams *et al.*, 1964; Johnson *et al.*, 1966; Takahashi *et al.*, 1969). At that time, Graham and Oppenheimer (1969) suggested that OPCA, Shy–Drager syndrome and SND often co-exist clinicopathologically and proposed the term multiple system atrophy (MSA). Following this paper, many other clinicopathological studies supported this view (Bannister and Oppenheimer, 1972; Borit *et al.*, 1975; Spokes *et al.*, 1979; Gosset *et al.*, 1983; Polinsky 1984; Riku *et al.*, 1984). The subsequent discovery of glial cytoplasmic inclusions then allowed the clear definition of MSA as a clinicopathological entity (Papp *et al.*, 1989; Nakazato *et al.*, 1990). Neuronal loss and gliosis in the cerebral cortex, putamen, caudate nucleus, external pallidum, substantia nigra, locus coeruleus, pontine nuclei, inferior olives, cerebellar Purkinje cells, corticospinal tracts and intermediolateral cell columns of the spinal cord have been assessed so far (Riku *et al.*, 1984; Sobue *et al.*, 1986, 1987, 1992; Kume *et al.*, 1991, 1993; Terao *et al.*, 1994; Wenning *et al.*, 1995, 1997; Lowe *et al.*, 1997). Based on these clinicopathological analyses, diagnostic criteria were proposed by a Consensus Conference in 1998 (Gilman *et al.*, 1999). This statement recommended designating patients as having MSA-P if parkinsonian features predominated or MSA-C if cerebellar features predominated, in lieu of the older designations SND and OPCA, respectively. The designation Shy–Drager syndrome was considered to have lost practical meaning because of wide misuse of the term. Furthermore, almost all MSA patients develop autonomic dysfunction at some point during their course.

The presence of autonomic failure/urinary dysfunction plus either parkinsonism poorly responsive to levodopa or cerebellar ataxia is necessary to establish a clinical diagnosis of MSA and distinguish it from other diseases (Litvan *et al.*, 1997; Mathias and Bannister, 1999; Gilman *et al.*, 1999). However, MSA patients often show motor impairment or autonomic symptoms in isolation during the initial phase, followed by additional features during the course of the illness. Recently, Gilman *et al.* (2000) reported that 17 of 51 sporadic OPCA patients evolved to MSA within 5 years, and that this transition carried a poor prognosis for survival. Since the prognosis of MSA is less favourable than that of hereditary ataxia or Parkinson's disease, defining the interval from onset of first symptom to concurrent multiple system impairment is important for making an accurate diagnosis, for counselling patients and family members with respect to prognosis, and for designing therapeutic trials. Furthermore, variability has been observed concerning patterns of MSA signs, symptoms and progression, specifics of autonomic

failure, MRI findings and ultimate prognosis. Many studies have suggested several risk factors that influenced progression and survival in MSA (Saito *et al.*, 1994; Schulz *et al.*, 1994; Wenning *et al.*, 1994; Testa *et al.*, 1996; Ben-Shlomo *et al.*, 1997; Klockgether *et al.*, 1998). However, some of these investigations involved small numbers of patients and, with the exception of three studies (Wenning *et al.*, 1994; Ben-Shlomo *et al.*, 1997; Klockgether *et al.*, 1998), diagnostic criteria were not uniform; thus proposed risk factors for progression and prognosis such as phenotype, gender or age of onset have shown disagreement between reports.

In addition, several reports have suggested that OPCA (MSA-C) is relatively more frequent and SND (MSA-P) less frequent among Japanese MSA patients than is the case in Western populations, but this generalization has not been assessed by current diagnostic criteria (Kita, 1993; Saito *et al.*, 1994). These observations, however, have raised the possibility that phenotypic manifestations of MSA may be influenced by ethnic background.

In this study, we investigated the initial clinical manifestation of MSA and subsequent evolution and outcome in 230 Japanese patients with probable or definite disease.

Methods

Selection of patients

We reviewed the medical records of 286 patients with a clinical diagnosis of MSA who were referred to the Nagoya University Hospital, Aichi Medical University Hospital or one of four affiliated hospitals in Aichi prefecture between 1985 and 1999. We evaluated these patients based on the Consensus Conference statement concerning MSA diagnostic criteria (Gilman *et al.*, 1999), and excluded 56 patients who did not fulfil criteria for probable or definite MSA. These excluded patients comprised: eight patients with cerebellar ataxia and parkinsonism but no autonomic involvement; 15 with orthostatic hypotension but failing to fulfil diagnostic criteria; and 11 with severe autonomic failure who did not develop parkinsonism or cerebellar signs during the follow-up period (two with mild rigidity and no gait disturbance; two with only postural tremor; three with nystagmus and mild limb ataxia; and four with extensor plantar responses and normoreflexia or hyper-reflexia). We also excluded 14 patients for whom we could not obtain the necessary information from medical records and interviews. Of the 230 MSA patients ultimately included in this study, all were followed-up by least one of the six institutions for a total period of 1–17 years (mean, 4.0 ± 2.8).

Clinical evaluation

The motor or autonomic symptoms initially noted by patients were considered to represent onset. Time from

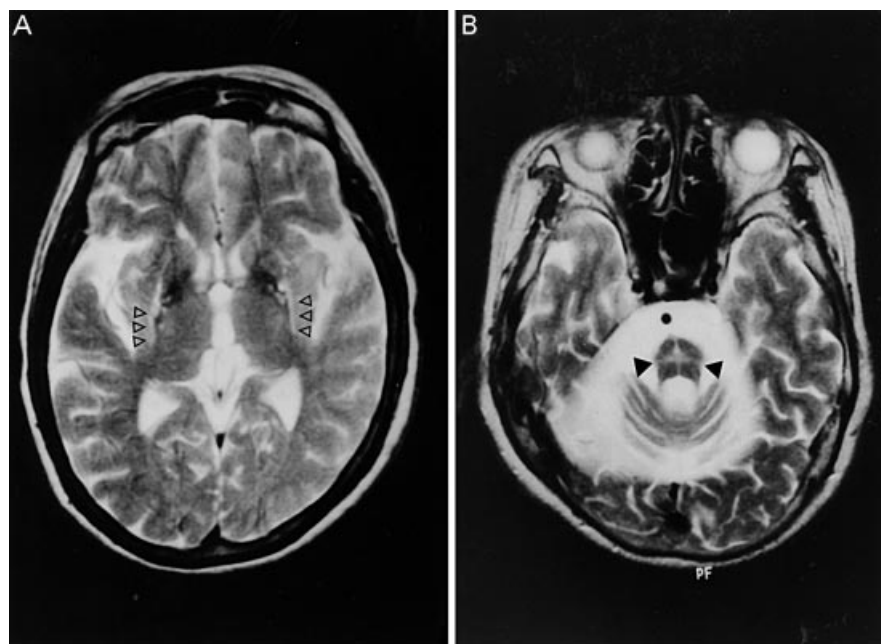


Fig. 1 MRI signal abnormalities in patients with multiple system atrophy. (A) Hyperintense putaminal rim on T₂-weighted images [1.5 T; 4000 ms repetition time (TR), 120 ms echo time (TE)] in the axial plane (arrowheads). (B) Signal change in the pons on T₂-weighted images (1.5 T; TR, 4000 ms; TE, 120 ms) in the axial plane (arrowheads).

Table 1 Patient characteristics

Characteristics	MSA	MSA-C	MSA-P
<i>n</i>	230	155	75
Male : female	131 : 99	93 : 62	38 : 37
Age at onset (years)	55.4 ± 8.3	54.8 ± 8.7	56.7 ± 7.2
Time from onset to diagnosis (years)	3.3 ± 2.0	3.2 ± 2.1	3.4 ± 1.7
Follow-up period (years)	4.0 ± 2.8	3.9 ± 2.7	4.0 ± 3.0
Initial symptoms			
Autonomic <i>n</i> (%)	64 (27.8)	49 (31.6)	15 (20.0)
Motor <i>n</i> (%) ^a	166 (72.2)	106 (68.4)	60 (80.0)

^aMotor symptoms include either parkinsonism or cerebellar ataxia.

onset to transition or evolution to MSA, requiring both motor and autonomic involvement, was defined as patient awareness of symptoms of both types. Symptoms of all 230 patients were assessed from clinical records, and confirmed by an interview of patients and family if adequate information was not obtained from clinical records. All the autopsy records were assessed for the patients who underwent post-mortem examination. Autonomic symptoms included urinary and orthostatic symptoms. Urinary symptoms were nocturnal or diurnal urinary frequency, a sensation of urgency, urinary incontinence, voiding difficulty and retention. Orthostatic symptoms were postural faintness, blurred vision or syncope associated with an orthostatic drop of 30 mmHg in systolic blood pressure or 15 mmHg in diastolic blood pressure without a corresponding increase

in heart rate of >10 beats per minute. While sexual impotence in MSA is a noteworthy symptom, manifesting in an early phase and affecting virtually all male patients, it was not considered here. Organic erectile failure can be difficult to distinguish objectively from psychogenic impotence (Mathias *et al.*, 1999). Furthermore, impotence has low specificity for diagnosis of MSA, as the consensus statement described (Gilman *et al.*, 1999).

We assessed three activities of daily living (ADL) milestones to evaluate disease progression: aid-requiring walking was defined as use at all times of a walking aid or a companion's arm for support; a wheelchair-bound state was defined as use of a wheelchair at all times; and a bedridden state was defined as complete loss of ability for independent movement. We assessed time of onset for each of these states and for death by reviewing the patient's record, by family

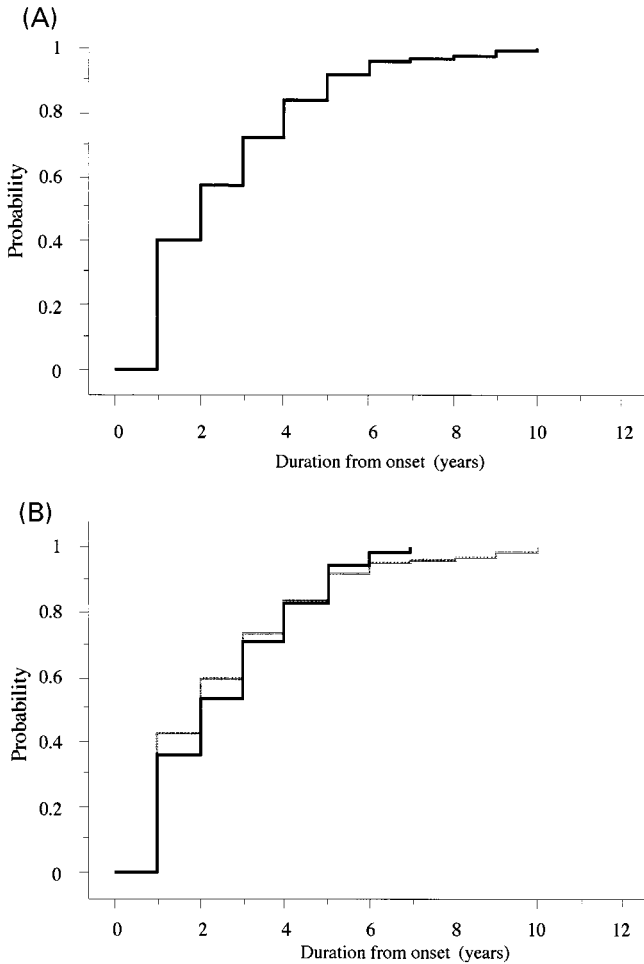


Fig. 2 Time from onset to appearance of concomitant motor and autonomic manifestations calculated by the Kaplan–Meier method. Patients are considered overall in **A** and by phenotypic group in **B**. No significant difference in rate of this evolution was noted between predominantly cerebellar multiple system atrophy (MSA-C; thin line) and predominantly parkinsonian (MSA-P; thick line).

interviews and direct examination of the patients in the follow-up hospital.

MRI

We examined MRI findings at the first hospital visit for 139 of 230 patients. Age at MRI examination ranged from 43 to 78 years (mean, 56.9 ± 8.1 years). Among these, 96 MSA patients (59 MSA-C, 37 MSA-P) were examined with a 1.5 T scanner, and 43 patients (26 MSA-C, 17 MSA-P) with a 0.5 T scanner. All MRIs included T₁- and T₂-weighted axial images [2300–4000 ms repetition time (TR), 80–120 ms echo time (TE), 5–8 mm thickness and 1–2.5 mm gap). We evaluated the presence of a hyperintense rim in the dorsolateral putamen (Fig. 1A) and a ‘hot cross bun’ sign in the pons (Fig. 1B)

according to previous reports (Savoirdo *et al.*, 1990; Konagaya *et al.*, 1994; Schrag *et al.*, 1998; Kraft *et al.*, 1999). We also quantified atrophic change of the cerebellar vermis (CV), pontine basis (PB) and corpus callosum (CC) in 52 patients with sufficient information available for assessment (33 MSA-C, 19 MSA-P; mean age, 55.7 ± 8.2 years; range, 42–78 years) compared with 45 age-matched control subjects (mean age, 55.1 ± 7.7 years; range, 42–76 years). A midsagittal T₁-weighted spin-echo image was used for measurement (1.5 T; TR, 350–500 ms; TE, 15–20 ms). Areas of CV, PB and CC were quantified from the computer monitor using US National Institutes of Health image software (version 1.60) as described previously (Abe *et al.*, 1998). Areas of the midline posterior fossa (MPF) and midline internal skull surface (MISS; inner table, foramen magnum, clivus, sellar diaphragm and jugum sphenoidale) were measured to adjust for individual variation in the size of the skull. Ratios of PB/MPF, CV/MPF and CC/MISS were calculated as previously described (Laissy *et al.*, 1993; Abe *et al.*, 1998).

Statistical analyses

Data were entered into a database for further statistical analysis. Kaplan–Meier analyses were used to estimate the disease progression assessed by ADL milestones. Risk factors possibly influencing disease progression included initial symptoms, age of onset, disease phenotype and gender. Log-rank test statistics were used to determine whether Kaplan–Meier transition curves differed among subgroups (Peto *et al.*, 1977). Statistically assessed data for disease progression are expressed as median values. The disease duration from onset to the time when both autonomic and motor impairment was present was also assessed as a risk factor. The Mann–Whitney *U* test was used to compare continuous variables for different subgroups. Contingency tables were analysed with the χ^2 test. Relationships between duration of cerebellar signs and interval from onset to degree of CV, PB and CC atrophy were analysed using Pearson’s correlation coefficient. Calculations were performed using the statistical software package Stat View (Abacus Concepts, Berkeley, Calif., USA).

Results

Patient characteristics

Patients consisted of 131 men and 99 women (Table 1). Mean age at onset of the first symptom was 55.4 ± 8.2 years (range, 38–75 years). 155 patients had MSA-C and 75 had MSA-P. No significant differences were noted between these two subgroups for gender distribution, age at onset, interval from onset to MSA diagnosis or follow-up period. 166 patients complained of motor disturbance as an initial symptom before appearance of autonomic failure; cerebellar dysfunction was the initial symptom in

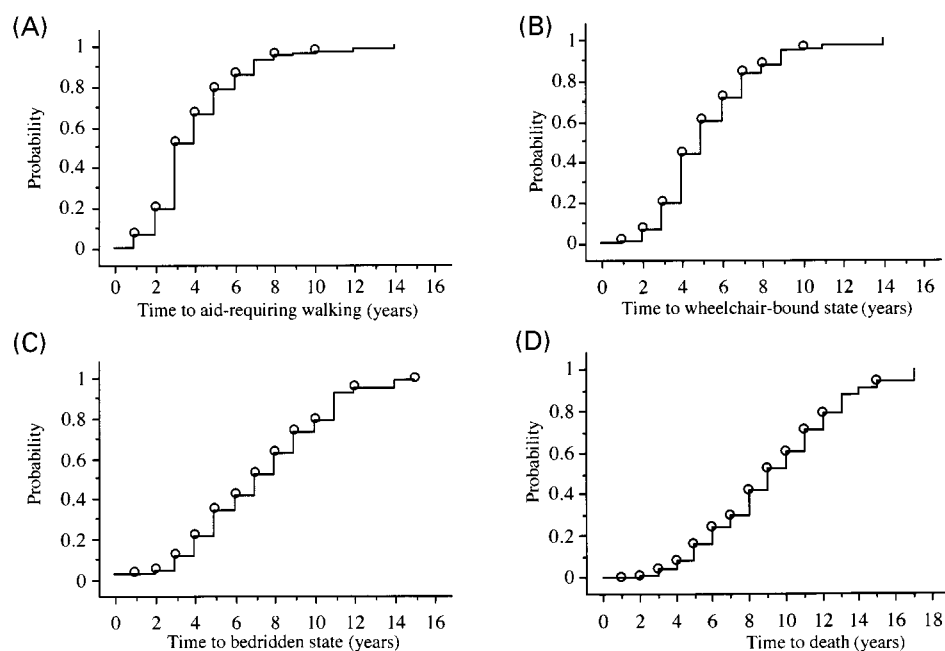


Fig. 3 Activities of daily living (ADL) as milestones indicating disease progression [aid-requiring walking (A), wheelchair-bound state (B), bedridden state (C)] as well as survival in patients (D) with MSA. Kaplan–Meier curves are shown.

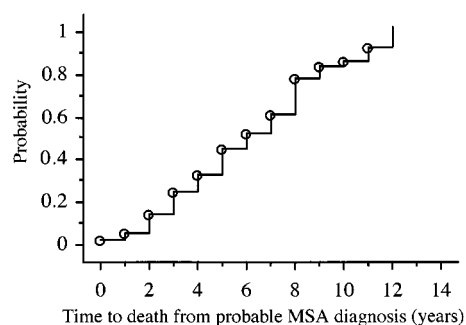


Fig. 4 Estimated time to death from the point of diagnosis of probable MSA. Kaplan–Meier curve.

105 of these patients, and parkinsonism in 61. Sixty-four patients showed autonomic failure as an initial symptom, with urinary symptoms in 44 and postural hypotension in 20. In the MSA-C group, 106 and 49 patients showed cerebellar dysfunction and autonomic failure as initial symptoms, respectively. In the MSA-P group, 60 and 15 patients noted parkinsonism and autonomic failure as initial symptoms, respectively. At diagnosis of MSA, bladder disturbance was evident in 187 patients (82.2%), and postural faintness, blurred vision or syncope was present in 69 (30.0%). Motor impairment versus autonomic failure as the initial symptom did not differ significantly between MSA-C and MSA-P.

Time from onset to evolution to MSA

A Kaplan–Meier estimated time curve from the initial onset to the presence of concomitant motor and autonomic manifestations (evolution from onset to clinical MSA) is presented in Fig. 2. In all MSA patients (Fig. 2A), the median period was 2.0 years (range 1–10 years) while frequency of concomitant manifestations at 2, 4 and 6 years was 57.4, 83.5 and 96.5%, respectively. No significant difference for this interval was noted by a log-rank test comparing MSA-C with MSA-P (Fig. 2B).

Progression, outcome and risk factors

Seventy-eight patients had died at the time of data collection. In 22 of these patients (13 MSA-C, nine MSA-P), autopsy was performed and the diagnosis of definite MSA confirmed. Pathological findings included neuronal loss and astrogliosis in the olivopontocerebellar, striatonigral and autonomic systems as well as corticospinal tracts. Glial cytoplasmic inclusions, a specific hallmark of MSA, were abundant in oligodendroglia as assessed by Gallyas–Braak staining. Figure 3 shows Kaplan–Meier estimates for ADL milestones including aid-requiring walking, wheelchair-bound state, bedridden state and death. These intervals were measured from the time of initial symptom onset. Tracheostomy was performed in 40 patients (23 MSA-C, 17 MSA-P) at 6.3 ± 3.0 years from onset; these patients were treated as censored data from the time of that operation. The median interval from

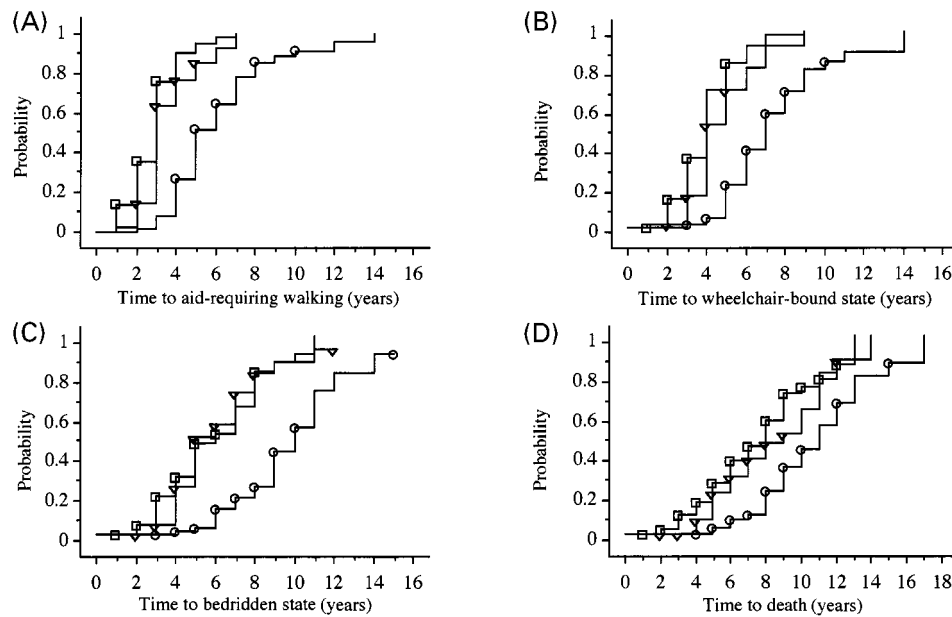


Fig. 5 Kaplan–Meier estimates and the log-rank test were used to compare survival as well as the occurrence of three milestones concerning activities of daily living (ADL) between three groups defined by interval from onset to evolution of concomitant motor and autonomic impairment. Squares, triangles and circles represent censored data, indicating subjects with evolution within 1 year, 2–3 years or after 3 years, respectively. Risk of progression to each ADL milestone or dying differed significantly between evolution rates: (A) aid-requiring walking, $P < 0.01$; (B) wheelchair dependence, $P < 0.01$; (C) bedridden state, $P < 0.01$; and (D) death, $P < 0.01$.

Table 2 Potential risk factors concerning progression and survival

	Aid-requiring walking		Wheelchair dependence		Bedridden state		Death	
	Median time (years)*	P value [†]	Median time (years)	P value	Median time (years)	P value (years)	Median time	P value
Duration								
≤3 years	5.0	<0.01	7.0	<0.01	10.0	<0.01	11.0	<0.01
>3 years	3.0		4.0		6.0		8.0	
Age at onset								
≤55 years	4.0	0.07	5.0	0.05	8.0	0.03	10.0	0.03
>55 years	3.0		4.0		7.0		8.0	
Type								
MSA-C	4.0	0.03	5.0	<0.01	8.0	<0.01	10.0	0.26
MSA-P	3.0		4.0		6.0		8.0	
Initial symptom								
AF/UD	4.0	<0.01	6.0	<0.01	8.0	0.27	9.0	0.92
Motor	3.0		5.0		7.0		9.0	
Gender								
Male	3.0	0.37	5.0	0.23	8.0	0.62	9.0	0.47
Female	3.0		5.0		7.0		9.0	

*Median survival was calculated by Kaplan–Meier estimates. [†]Log-rank test statistics were used to determine whether Kaplan–Meier transition curves differed among subgroups. AF/UD = autonomic failure/urinary dysfunction.

onset to aid-requiring walking, wheelchair requirement, bedridden state and death was 3, 5, 8 and 9 years, respectively. The frequency of patients with aid-requiring

walking, wheelchair requirement and bedridden state within 5 years of initial onset was 78.4, 59.4 and 31.6%, respectively. Survival rates at 5 and 10 years were 83.5 and 39.9%. The

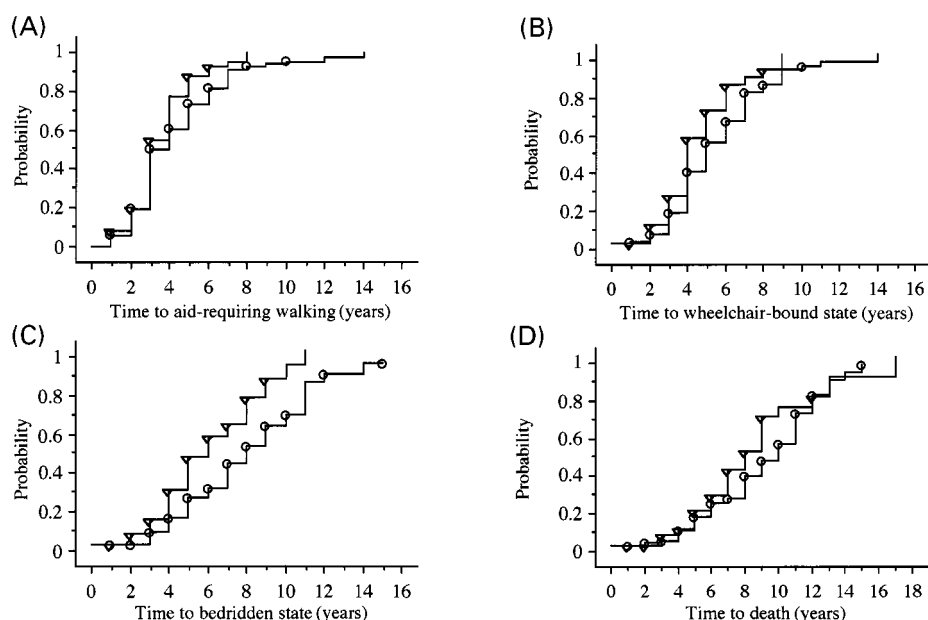


Fig. 6 Difference in time remaining free from three activities of daily living (ADL) milestones as well as survival between MSA-C and MSA-P. Triangles and circles represent censored data, indicating subjects with MSA-P and MSA-C, respectively. Significant differences were seen between the two groups for the three ADL milestones but not for survival by a Kaplan–Meier analysis and the log-rank test: (A) aid-requiring walking, $P = 0.03$; (B) wheelchair dependence, $P < 0.01$; (C) bedridden state, $P < 0.01$; (D) death, $P = 0.26$.

estimated time to death from the point at which patients were diagnosed as probable MSA was 6.0 years, calculated by the Kaplan–Meier method (Fig. 4).

Figure 5 represents the Kaplan–Meier curves of three ADL milestones and of survival estimated in terms of time from initial symptom onset to evolution to MSA including three subgroups: within 1 year, from 1 to 3 years and >3 years. Subgroups representing shorter times from onset to concomitant motor and autonomic system impairment, particularly times not exceeding 3 years, progressed more rapidly to each ADL milestone and to death. These differences were significant by a log-rank test for comparison between evolution-defined subgroups ($P < 0.01$). These results indicate that the shorter the time from onset to evolution to MSA phenotype, the more rapid the progression in ADL milestones and eventual death.

Risk factors evaluated concerning progression and survival are summarized in Table 2. Time from onset to evolution to MSA, age of onset, disease phenotype (MSA-C versus MSA-P) and initial symptom (autonomic versus motor) influenced either progression to ADL milestones or survival to some degree. Patients with concomitant motor and autonomic involvement (evolution time to MSA) within 3 years of onset had a significantly greater risk of entering an advanced disease stage as well as poorer survival than those with a more gradual evolution to MSA. Onset in older individuals also increased the risk of ADL functional deterioration and death. In contrast, MSA-P patients had more rapid functional

deterioration than MSA-C patients, but showed similar survival (Fig. 6). Patients whose symptoms of motor impairment preceded autonomic failure had an accelerated risk of requiring walking aid and a wheelchair, but the time until confinement to bedridden state and the survival was no worse. Gender was not predictive of either progression to a more advanced ADL milestone or survival.

Evaluation of MRI abnormalities

Patients who underwent MRI evaluation included 85 with MSA-C and 54 with MSA-P. Neither interval from onset to MRI examination nor gender differed significantly between MSA-C and MSA-P (Table 3).

A hyperintense rim at the lateral edge of the dorsolateral putamen was evident in 31 (32.2%) of 96 patients with MSA on 1.5 T images and 17 (39.5%) of 43 on 0.5 T images. The ‘hot cross bun’ sign was seen in the pons in 62 (64.5%) of 96 patients on 1.5 T scans and 26 (60.4%) of 43 on 0.5 T scans. Thus the frequency of signal abnormalities was not significantly different between 1.5 T and 0.5 T. With regard to clinical phenotype, the frequency of putaminal abnormality in MSA-P was higher than in MSA-C, and the frequency of pontine abnormality in MSA-C was higher than in MSA-P. MRI signal abnormalities became more frequent with increasing disease duration from onset of the initial symptom and from onset of motor impairment (Table 4).

Table 3 MRI abnormalities and disease duration from onset to autonomic or motor impairment

	MSA	MSA-C	MSA-P
1.5 T			
Duration (years)	3.9 ± 2.3	3.8 ± 2.3	4.2 ± 2.4
n (male : female)	96 (54 : 42)	59 (34 : 25)	37 (20 : 17)
MRI findings			
Pontine abnormality n (%)	62 (64.5)	48 (81.4)	14 (37.8)
Putaminal abnormality n (%)	31 (32.2)	10 (16.9)	21 (56.8)
0.5 T			
Duration (years)	4.3 ± 2.3	4.2 ± 2.5	4.6 ± 2.2
n (male : female)	43 (24 : 19)	26 (14 : 12)	17 (10 : 7)
MRI findings			
Pontine abnormality n (%)	26 (60.4)	20 (76.9)	6 (35.3)
Putaminal abnormality n (%)	17 (39.5)	6 (23.1)	11 (64.7)

The frequency of pontine signal abnormalities in MSA-C was higher than that of putaminal signal abnormalities in MSA-P.

Table 4 Symptom duration and frequency of MRI signal abnormality

	Frequency of pontine abnormality in MSA-C (%)		Frequency of putaminal abnormality in MSA-P (%)	
	Time from onset	Time from motor impairment	Time from onset	Time from motor impairment
≤2 years	78.9	64.0	38.1	38.5
≤4 years	76.2	87.5	65.0	72.2
>4 years	92.9	100	76.9	80.0

Morphometric MRI analysis revealed significant decreases in ratios of CV/MPF, PB/MPF and CC/MISS in patients with MSA compared with control subjects ($P < 0.01$), and the CV/MPF and PB/MPF ratio in patients with MSA-C was significantly smaller than in patients with MSA-P ($P < 0.01$; Fig. 7). The CC/MISS ratio was not significantly different between MSA-C and MSA-P. Both CV/MPF and PB/MPF ratios showed significant negative correlations with disease duration from onset ($r = 0.39$, $P < 0.01$ and $r = 0.44$, $P < 0.01$, respectively; Fig. 8A and B), while the CC/MISS ratio did not show a correlation with duration from onset ($r = 0.10$, $P > 0.5$; Fig. 8C). In patients with MSA-C, a more significant negative correlation was seen between disease duration from onset of cerebellar signs and CV/MPF ($r = 0.71$, $P < 0.01$; Fig. 8D) and PB/MPF ($r = 0.76$, $P < 0.01$; Fig. 8E). When progression of atrophy was assessed on the individual patients, a decrease in CV/MPF, PB/MPF was associated with both disease duration and ADL milestone progression but was highly variable for each ADL milestone between individual patients (Fig. 9).

Discussion

In this study, the calculated median time from onset to evolution to MSA was 2.0 years. Within 4 years, 85% of patients showed both autonomic failure and motor impairment. Median survival time was 9.0 years and ranged from 2

to 17 years, in good agreement with previous studies (Wenning *et al.*, 1994; Klockgether *et al.*, 1998). Our study further documented that rate of progression to multiple system involvement varied among patients but was independent of age of onset, clinical phenotype, initial symptom and gender. Median times from onset to aid-requiring walking, wheelchair requirement and a bedridden state were 3.0, 5.0 and 8.0 years, respectively, as calculated by Kaplan–Meier analysis.

Various factors have been proposed to predict survival in MSA, including gender, age of onset and clinical phenotype (Saito *et al.*, 1994; Schulz *et al.*, 1994; Wenning *et al.*, 1994; Testa *et al.*, 1996; Ben-Shlomo *et al.*, 1997; Klockgether *et al.*, 1998); however, disagreements were evident between these reports. In this study, gender was not associated with worsening of ADL milestones or survival. Wenning *et al.* (1994) previously indicated that gender influenced survival time when early manifestation of sexual dysfunction in men was included as one of the initial symptoms, but gender had no influence when only motor symptoms were considered as an initial symptom. The absence of a gender effect in our results could have been due to excluding sexual dysfunction as an initial symptom. Whether the phenotypes of MSA-P and MSA-C differentially affect survival is controversial (Saito *et al.*, 1994; Schulz *et al.*, 1994; Wenning *et al.*, 1994; Testa *et al.*, 1996; Ben-Shlomo *et al.*, 1997). We found that MSA-P patients had accelerated deterioration with respect to ADL

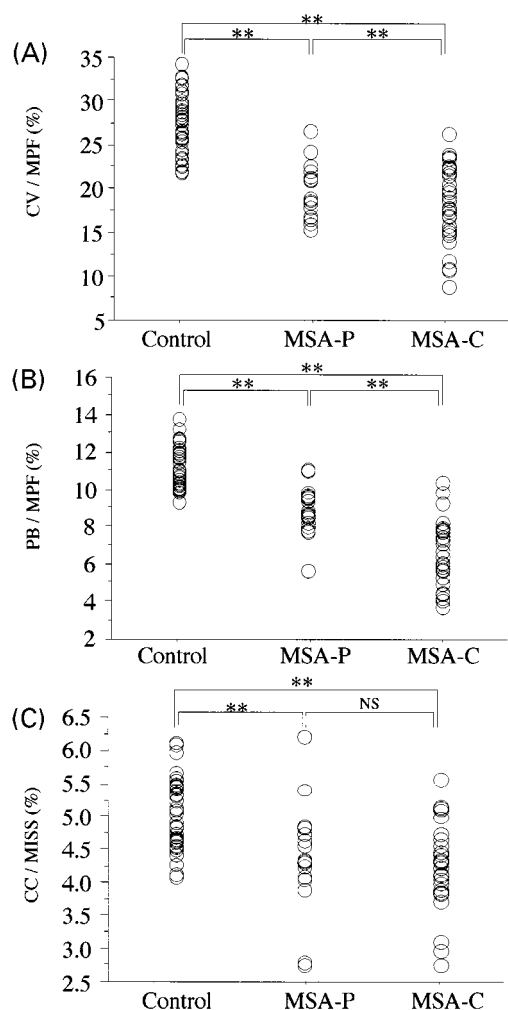


Fig. 7 Relationship between size ratios of brain regions to skull regions (A) CV/MPF; (B) PB/MPF; and (C) CC/MISS (inner table, foramen magnum, clivus, sellar diaphragm, jugum sphenoidale) in patients and control subjects. CV/MPF, PB/MPF and CC/MISS in MSA patients were significantly smaller than in control subjects. The CV/MPF and PB/MPF ratios in MSA-C were much smaller than in MSA-P. The CC/MISS ratio did not differ between MSA-C and MSA-P. ** $P < 0.01$ by Mann-Whitney U test. NS = not significant.

milestones compared with MSA-C, while survival was no worse. Our results may suggest that parkinsonism affects motor aspects of ADL more profoundly than cerebellar dysfunction. In contrast to gender and clinical phenotype, higher age at onset increased risk of death, in agreement with most previous reports (Wenning *et al.*, 1994; Ben-Shlomo *et al.*, 1997).

A striking observation in our study was that a shorter time of evolution to MSA predicted worse deterioration of ADL and shorter survival. In particular, evolution to MSA within 3 years from onset strongly predicted an aggressive course. Gilman *et al.* (2000) reported that the median life expectancy from symptom onset was 20.7 years in a group with pure cerebellar ataxia, but only 7.7 years in a group with cerebellar

ataxia plus non-cerebellar symptoms, particularly parkinsonism; thus the appearance of non-cerebellar symptoms carried a poor prognosis for survival in cerebellar ataxia. This group with pure cerebellar ataxia plus non-cerebellar symptoms was considered to represent MSA (Gilman *et al.*, 2000). Our study indicated that time from initial symptom to appearance of other symptoms indicating evolution to MSA was strongly related to deterioration of ADL and worsening of survival. Although our observation is somewhat similar to that of Gilman *et al.*, in that evolution from single-system impairment to impairment of multiple systems affects survival, our study indicated that early evolution is particularly important for predicting ADL deterioration and poor survival. Why some patients show early evolution to MSA while others show a long interval of restricted system impairment is not known. One possible explanation involves differences in genetic background. Recent studies suggest that widespread accumulation of α -synuclein plays an important role in the pathogenesis of MSA, and possibly in evolution of dysfunction to involve multiple systems (Tu *et al.*, 1998; Dickson *et al.*, 1999). However, polymorphism of various genes including the α -synuclein gene showed no evident effect on development of MSA (Morris *et al.*, 2000). Genetic variation of as yet unidentified genes could be related to evolution time, and much further study is needed to solve these issues.

MRI is a useful procedure not only for diagnosis but also for investigating clinical features of MSA (Stern *et al.*, 1989; Savoirdo *et al.*, 1990; Kume *et al.*, 1992; Konagaya *et al.*, 1994; Wakai *et al.*, 1994; Schrag *et al.*, 1998, 2000; Kraft *et al.*, 1999). A hyperintense putaminal rim and a 'hot cross bun' sign on T_2 -weighted images are characteristic MRI signs of MSA (Konagaya *et al.*, 1994; Schwarz *et al.*, 1996; Schrag *et al.*, 1998, 2000). The occurrence of signal abnormalities in the putamen and pons was not significantly different between 1.5 T and 0.5 T examinations, in agreement with previous studies (Schrag *et al.*, 1998, 2000). We found a good correlation between prevalence of signal abnormality and disease duration. Both the putaminal and pontine abnormalities on MRI were significantly accentuated as MSA-P and MSA-C features advanced. Thus, these MRI findings were useful markers for assessing the MSA-P and MSA-C pathology, complementing clinical follow-up examination.

The diagnostic utility of signal abnormality in early MSA remains unclear. In particular, the frequency of a putaminal abnormality in MSA-P was lower than that of pontine abnormalities in MSA-C in all stages. Less prevalent putaminal than pontine abnormality in our series may correspond to a smaller proportion of patients with MSA-P than MSA-C or, alternatively, could be due to a putaminal pathological feature. Iron content in the posterolateral part of the putamen has been reported to increase in MSA (Boritt *et al.*, 1975; Vymazal *et al.*, 1999). Thus, a hyperintense putaminal rim signal in MSA-P could be masked by hypointensity due to iron accumulation, particularly in some patients with advanced disease. Further prospective

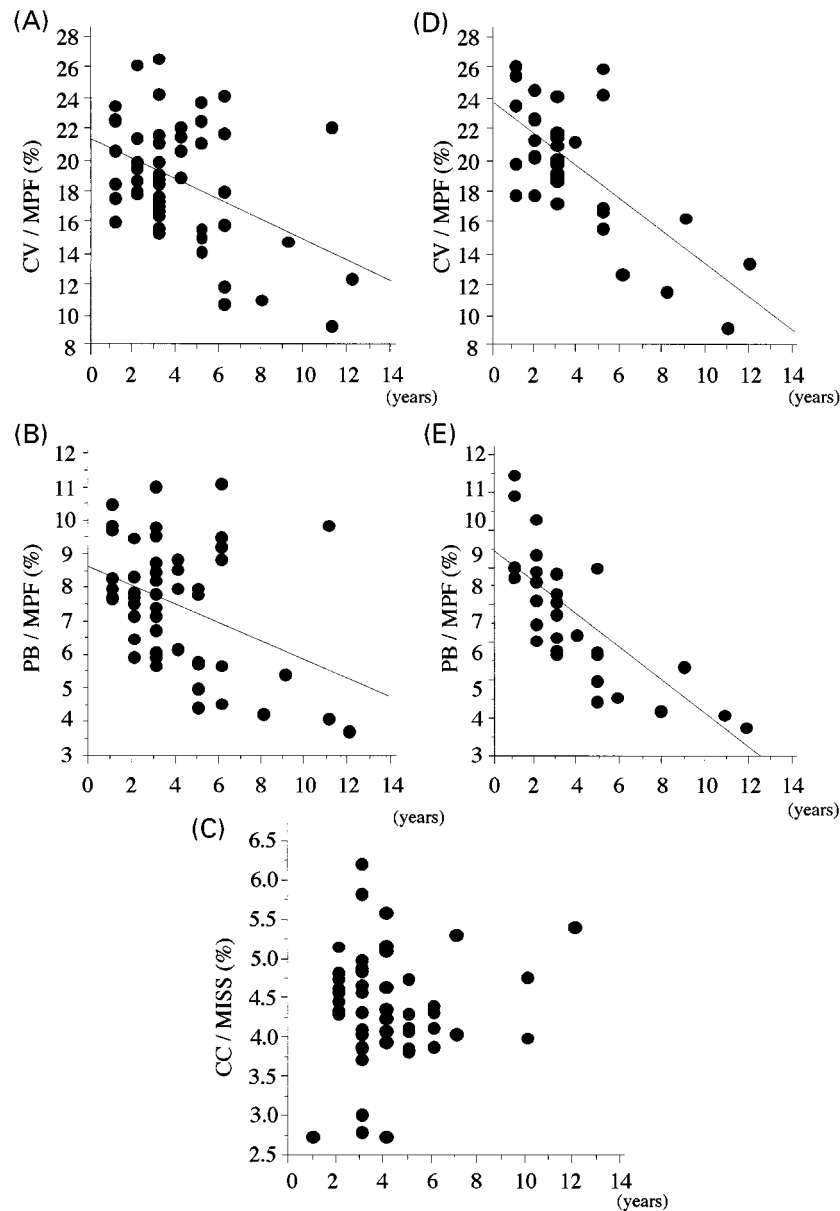


Fig. 8 Relationship between atrophy and disease duration from onset of illness. Significant correlations were seen between duration and both CV/MPF (A) and PB/MPF (B), but not between duration and CC/MISS (C). Relationships between (D) CV/MPF and (E) PB/MPF and disease duration from onset of cerebellar signs in patients with MSA-C showed a more significant negative correlation (CV/MPF, $r = 0.71$, $P < 0.01$; PB/MPF, $r = 0.76$, $P < 0.01$) than disease duration from onset of other symptoms including autonomic failure.

longitudinal MRI assessments will be needed to solve this problem.

The degree of both CV and PB atrophy in patients with MSA-C was more significant than in patients with MSA-P, as in previous reports (Schulz *et al.*, 1994). Although the degrees of both CV and PB atrophy were markedly related to time from onset, CC/MISS varied considerably between cases and was not related to disease duration. Despite this absence of correlation between

degree of callosal atrophy and interval from onset, a subgroup of patients showed significant atrophy of the CC. In patients with apparent CC atrophy, cerebral atrophy was also conspicuous. Cerebral atrophy has been reported in cases of MSA with particularly long follow-up periods (Konagaya *et al.*, 1999; Horimoto *et al.*, 2000). Since glial cytoplasmic inclusions have been observed in the cerebral hemisphere (Papp *et al.*, 1994), cerebral peduncle (Yasui *et al.*, 1999) and CC (Costa

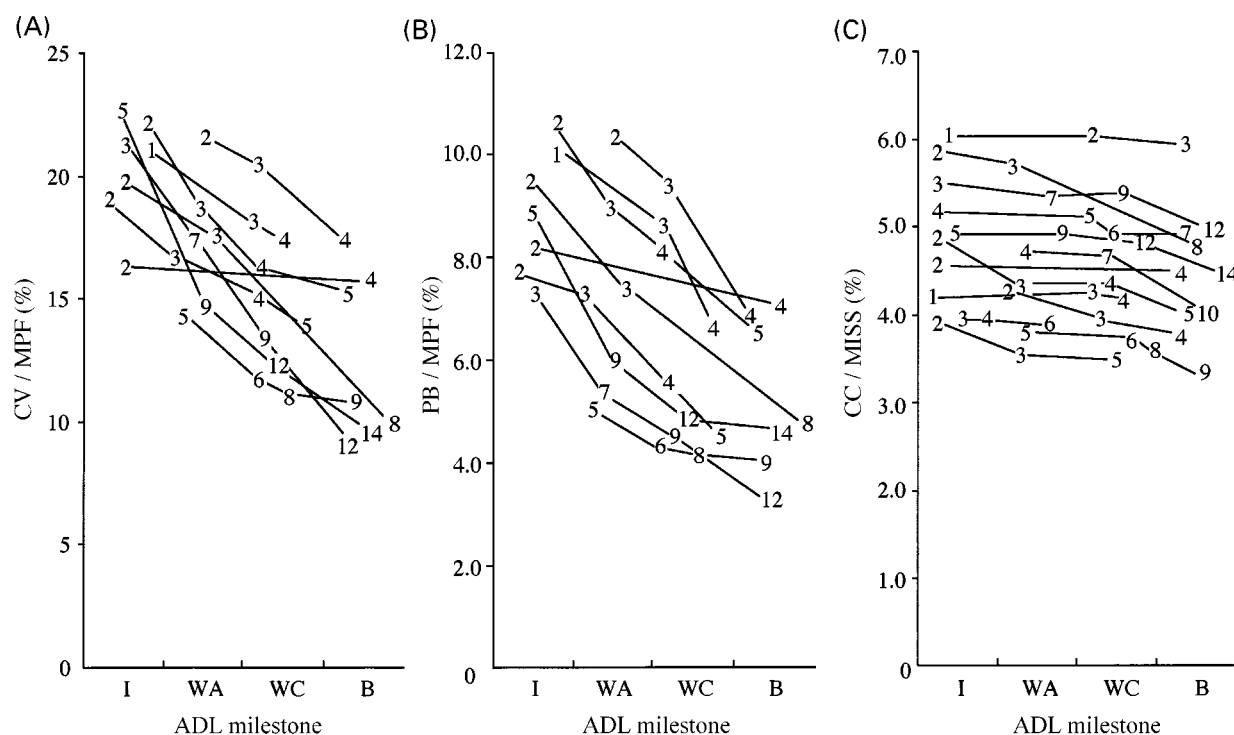


Fig. 9 Longitudinal study of (A) CV/MPF, (B) PB/MPF and (C) CC/MISS ratio in patients with MSA-C. Numbers represent time of MRI as years from disease onset. The CV/MPF, PB/MPF and CC/MISS ratios decreased in association with both disease duration and ADL deterioration. The decrease in CC/MISS in terms of ADL deterioration was less significant as compared with those in CV/MPF and PB/MPF. The CV/MPF, PB/MPF and CC/MISS ratios were variable at each ADL milestone. I = independent gait; WA = aid-requiring walking; WC = wheelchair dependence; B = bedridden state.

et al., 1992), these structures could be expected to atrophy in some MSA patients, as documented in this study. Our result suggests that a subgroup of MSA patients has a tendency toward cerebral hemispheric involvement, even though the cerebellum, pons and putamen are involved more frequently in MSA than the cerebral hemispheres. Evaluation of higher cognitive functions combined with MRI and other neuroimaging procedures in MSA patients should shed light on this problem.

We investigated the correlation between the degree of CV or PB atrophy and interval from clinical onset of evidence of cerebellar dysfunction to MRI, as well as the correlation of such atrophy with ADL deterioration in patients with MSA-C. Decreases in both CV and PB areas correlated strongly with time from onset of cerebellar symptoms, and were related to ADL deterioration to some extent. However, ADL deterioration was highly variable among the individual patients, and both motor ability and functional status did not strictly correspond to the atrophy. Other factors such as the rate of evolution to MSA, age at onset and clinical phenotype could also profoundly influence ADL deterioration, as described in this study.

Wenning *et al.* (1994) reported that MSA-P was the most common manifestation of MSA in a Western population (13.6%), and this finding was supported by some other studies (Testa *et al.*, 1996; Ben-Shlomo *et al.*, 1997). However, the frequency of MSA-C in two reports from Germany (Schulz *et al.*, 1994; Klockgether *et al.*, 1998) was 65.6 and 64.2%, respectively. In the present series, the proportion of MSA-C among Japanese MSA patients was also high (67.4%) and, correspondingly, MSA-P was relatively infrequent (32.6%). Sporadic spinocerebellar degeneration cases predominate over hereditary cases in Japan (2 : 1) (Kita, 1993), in contrast to the findings in Western studies (sporadic : hereditary, 1 : 3) (Polo *et al.*, 1991). In Japan, the percentage of OPCA patients among all spinocerebellar ataxia patients is relatively high (34.4%) (Kita, 1993), although diagnostic criteria used in reports differed from those of Western countries. MSA-C patients in this study had not only late-onset cerebellar ataxia but also additional features, including autonomic failure, fulfilling widely accepted clinical criteria. They did not simply have undifferentiated idiopathic late-onset cerebellar ataxia (Gilman *et al.*, 1996), and did not have features pointing to any other cause. Furthermore, the frequencies of MRI signal

abnormalities in MSA-C were similar to those previously reported (Schrage *et al.*, 1998, 2000), and 13 MSA-C patients examined at autopsy showed typical pathological features. The MSA-C patients in our series thus were considered to have the same clinicopathological nature as those in series from Western countries (Klockgether *et al.*, 1990; Gilman *et al.*, 1996). Although phenotypic differences could be due to physicians' referral patterns, the evidence suggests that the frequency of MSA phenotypes could differ between ethnic populations. Clinico-epidemiological and correlative data comparing MSA between Japanese and Caucasian populations currently are incomplete, but an analysis of ethnic background should be very informative concerning clinical phenotype, disease progression and prognosis of MSA. Factors determining clinical phenotype and evolution of system involvement in MSA are not clear at present, but genetic factors need further exploration.

Acknowledgements

We wish to thank Dr Terunori Mitsuma, Division of Neurology, Fourth Department of Internal Medicine, Aichi Medical University, Japan; Drs Tsutomu Yanagi, Shigetaka Hakusui and Keizo Yasui, Department of Neurology, Nagoya Daini Red Cross Hospital, Japan; Dr Takako Yamada, Department of Neurology, Chubu National Hospital, Japan; and Dr Akiko Yamaoka, Department of Neurology, Higashi Nagoya National Hospital, Japan, for valuable advice and kind suggestions. This work was supported by a COE grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and grants from the Ministry of Health, Labour and Welfare of Japan.

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Received July 23, 2001. Revised December 4, 2001.

Accepted January 7, 2002