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Prospective 5-year natural history study of probable MSA in 175 North American subjects

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OBJECTIVE

To examine disease progression and survival in 175 patients with probable multiple system atrophy (MSA) as defined by the first consensus conference (Gilman et al, 1999). The subjects were studied prospectively to determine (a) life expectancy as a guide to designing pharmacologic interventions and (b) whether there is a difference in course between subjects who, at entry, show cerebellar ataxia and autonomic failure without parkinsonian features (MSA-C) as compared to those with parkinsonian features and autonomic failure without cerebellar ataxia (MSA-P) and subjects with mixtures of parkinsonian and cerebellar features plus autonomic failure (MSA-PC).

BACKGROUND

Previous studies of the natural history of MSA have been retrospective. This prospective study of the disorder was designed to examine natural history in subjects who entered the study with the diagnosis of probable MSA. As the subjects entered the study at variable times after qualifying for the diagnosis of probable MSA, the onset of the disorder was taken as the date of the initial symptom.

METHODS

We examined at six-month intervals 175 patients with probable MSA recruited from 11 US sites. On entry, based upon clinical findings, the subjects were divided into three groups, MSA-C (purely cerebellar ataxia), MSA-P (purely parkinsonian features) and MSA-PC (mixed parkinsonian and cerebellar findings). The onset of the disorder in each subject was tracked back to the time that the relevant neurological symptoms first began. Longitudinal follow-up after entry included evaluations with UMSARS I, II, III, IV, COMPASS, and SF-36. Patients with MSA-C survived for a maximum of 13 yrs and a median of 3.9 yrs from symptom onset. Patients in both MSA-P and MSA-PC survived for a maximum of 19 yrs and a median time of 5.8 and 4.2 years, respectively. We analyzed data using a Kaplan-Meier Survival Analysis, and as the analysis needed to account for delayed entry (date of symptom onset and entrance into the study), the survival analysis was based on left truncated data.

RESULTS

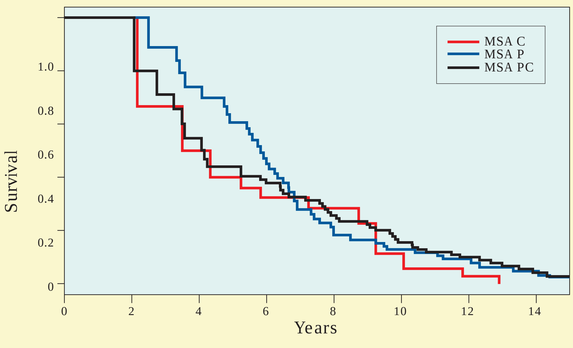
The study group consisted of 105 (60%) males and 70 (40%) females, mean age at entry 63.4 ± 8.6 yrs. Six cases dropped out after the initial screening and enrollment, hence we followed 169 subjects, including 19 patients with MSA-C, 70 with MSA-P, and 80 with MSA-PC (Table). Currently, 102 subjects have died and 67 are censored (alive and enrolled or lost to follow-up). Among those who expired, 40 received autopsy examination, with verification of diagnosis in 33. (One patient had diffuse Lewy body disease and the results are pending in six). The data reveal no difference in survival for the three groups (p = 0.47). The hazard of death is slightly higher for MSA-P than for MSA-C subjects (HR = 1.07, 95% CI = 0.55-2.1), but the hazard of death is less for MSA-PC than for MSA-C (HR = 0.88, 95% CI = 0.45-1.7); however, neither of these comparisons is statistically significant (p = 0.8 and 0.7, respectively. The results demonstrate that MSA is a rapidly lethal disorder in a substantial percent of subjects. By 5 years after initial symptom onset, approximately 50% of subjects with all three categories of subjects had expired. Hence pharmacological trials should enroll subjects at the earliest possible time after symptom onset.

Table. Overall outcome of subjects with MSA-C, MSA-P and MSA-PC

Type	Total N	Total Events	Total Censors	Total Arrivals	Total Missing	Total Survival
MSA-C	19	111	8	19	0	3.9
MSA-P	70	45	25	70	0	5.8
MSA-PC	80	46	34	80	0	4.2
	169	102	67	169	0	

Total Events = number of deaths; Total Censors = number of subjects still living or lost to follow-up; Total Arrivals = number of events + censors; Total Missing = cases not accounted for; Median Survival = median life span in years

Figure. Kaplan-Meier data for three MSA groups



CONCLUSIONS

This first large North American study of MSA revealed substantially larger numbers of MSA-P than MSA-C subjects, similar to the distribution reported in Europe and different from the distribution in Japan. The higher percent of men than women in this study is similar to previous studies from Europe. The prospective aspect of this study is valuable in providing information regarding the large variation in survival times from initial symptom onset, but the short median time to death fortifies the current view of MSA as a rapidly progressive fatal disease.

Reference

Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, Kaufmann H, Klockgether T, Lang AE, Lantos PL, Litvan I, Mathias CJ, Oliver E, Robertson D, Schatz I, Wenning GK. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999;163:94-98

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