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ORIGINAL ARTICLE

Longitudinal study of a cohort of MSA-C patients in South Italy: survival and clinical features

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Abstract

Sixty-six patients with possible or probable MSA (multiple system atrophy) cerebellar type, personally observed between 2006 and 2018 were retrospectively reviewed. The time point of data collection was January 1, 2019. Forty-nine patients lost independent walking after a median time of 5 years (95% C. I. 4–6). Thirty-two patients were confined to wheelchair after a median time of 7 years (95% C. I. 7–8). Twenty-seven patients were deceased after a median time of 9 years (95% C. I. 8–10). A later onset predicted an earlier loss of independent walking (HR 1.07; 95% C.I. 1.03–1.11; $p = 0.001$). Higher UMSARS score predicted shorter time to loss of independent walking (HR 1.04; 95% C.I. 1.02–1.06; $p = 0.001$) and to wheelchair (HR 1.03; 95% C.I. 1.01–1.06; $p = 0.021$). No predictor of time to death was found.

Keywords Multiple system atrophy · Survival · Predictors

Introduction

Multiple system atrophy (MSA) is a progressive fatal neurodegenerative disorder causing parkinsonism, cerebellar ataxia, autonomic and pyramidal dysfunction in various combinations. Two major forms of the disease are recognised, the parkinsonian (MSA-P) and the cerebellar (MSA-C). The age-adjusted prevalence for MSA, including probable and possible cases, is 4.4 per 100.000 (95% C.I. 1.2–7.6) [1]. Parkinsonian subtype is twice as prevalent as MSA-C in North America [2] and in Europe [3], whereas MSA-C is more common than MSA-P in the Japanese population [4]. Hence, it is not surprising that the majority of the studies is focused on MSA-P.

With regard to the natural history of the disease, about twenty prospective or retrospective studies are available [5]. They all considered both MSA-P and MSA-C. The mean age at onset varied from 53 to 63 years [6–8], the median time to wheelchair from 5 to 6.7 years [4, 8–10] and the median time to death from 6.2 to 10 years [6, 7, 11–13]. A recent meta-analysis identified as unfavorable predictors of survival severe dysautonomia and early development of combined autonomic and motor features, early falls and scores at clinical scales but not gender. There was conflicting evidence regarding the prognostic effect of age at onset and stridor [5].

The aims of this study are to evaluate clinical features, disease progression and survival and to identify variables that may modify the rate of disease progression in an ethnically homogeneous sample of Italian MSA-C patients.

Patients and methods

We retrospectively reviewed a cohort of 66 MSA-C patients from Southern Italy, most of them from Campania, the largest region in term of population in Southern Italy with 5.8×10^{-5} inhabitants [14]. The time point of data collection was January 1, 2019. They were observed at the Department of Neurology, Federico II University of Naples, between 2006 and 2018. Fifty-eight (87.9%) patients were diagnosed as probable, and eight (12.1%) as possible MSA-C according to current consensus diagnostic criteria [15].

Maria Lieto, Alessandro Roca and Dario Bruzzese contributed equally to this work.

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Clinical milestones were evaluated by using the Inherited Ataxia Progression Scale (IAPS) which defines phase 3 as loss of independent walking and phase 4 as the confinement to wheelchair [16]. Clinical features were estimated using the Unified Multiple System Atrophy Rating Scale (UMSARS) [17]. All patients performed brain magnetic resonance imaging and 29 patients DaT-Scan. Thirty patients received neuropsychological examination.

Baseline variables included demographic factors (gender, possible or probable diagnosis and age at onset), clinical signs (nystagmus, dysarthria, tremor [all types], bradykinesia, rigidity, increased tendon jerks, increased tone at lower limbs, Babinski signs, urinary incontinence, orthostatic hypotension, erectile dysfunction, dysphagia, stridor and REM behavior disorder) and imaging findings (atrophy of the cerebellum and pons, hot bun sign and putamen rim). Onset was defined as the time of first motor or autonomic symptoms as defined by the consensus criteria [15]. Orthostatic hypotension was defined as an orthostatic decrease in blood pressure by at least 30 mmHg systolic or 15 mmHg diastolic within 3 min of standing. Three outcome

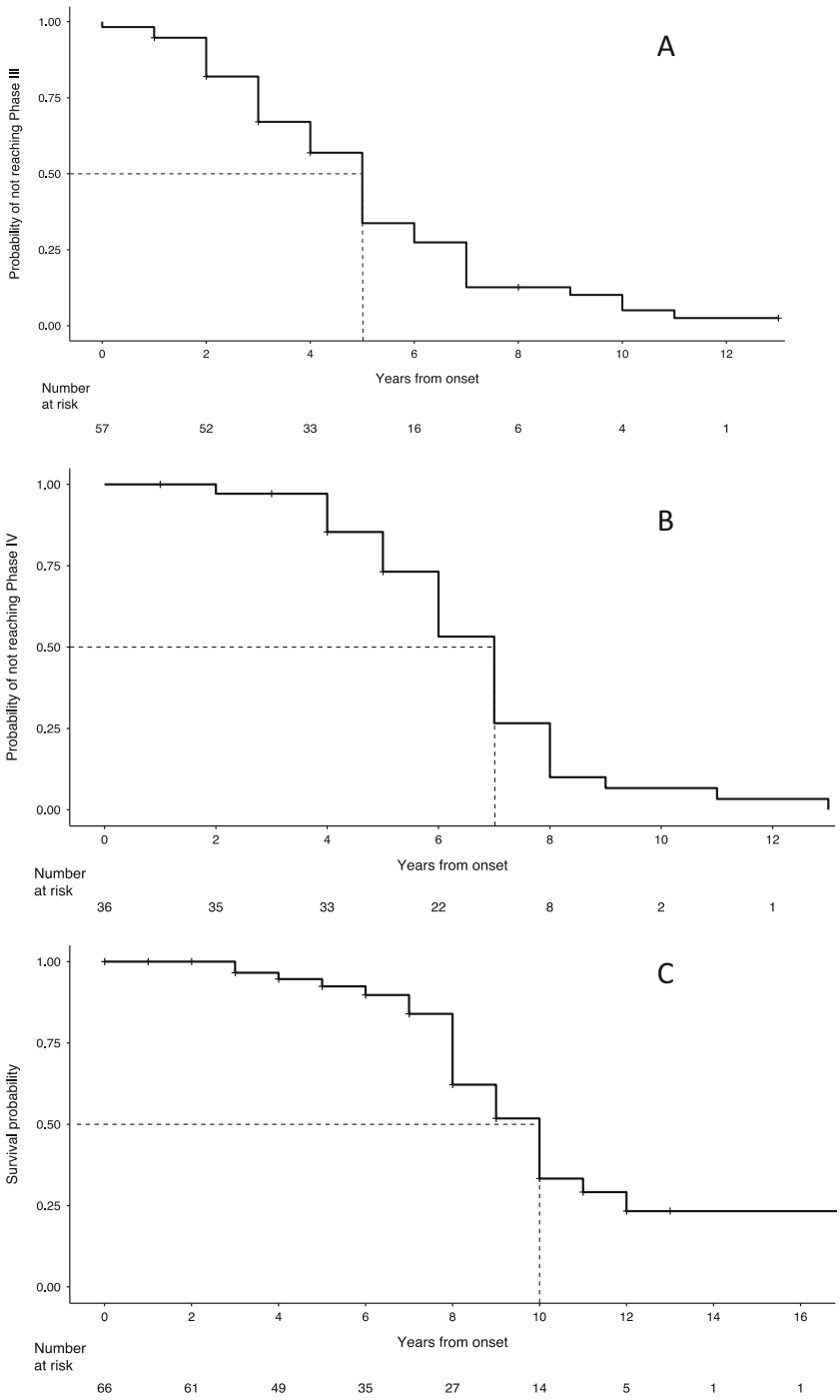

Fig. 1 The Kaplan-Meier survival curves for loss of independent walking (**a**), confinement to wheelchair (**b**) and death (**c**) in MSA-C patients

variables were defined: time to loss of independent walking (IAPS phase 3), time to wheelchair bound (IAPS phase 4) and time to death from onset of the disease.

Disease progression to loss of independent walking and to wheelchair was personally observed in most patients. Vital status was unknown for 18 patients. Follow-up was carried on until December 2018 or through death age for deceased patients. Information about the date and the causes of death was obtained from spouses or first degree relatives by personal interviews.

Numerical variables were described using either mean ± SD (in case of symmetrical distribution) or using the median (25th–75th percentile) when a consistent skewness was observed in exploratory analysis. Survival was defined as the time between onset and death (or loss of independent walking or wheelchair) or last assessment for censored patients. The median follow-up was computed according to the reverse Kaplan-Meier method. The analysis was graphically represented by the Kaplan-Meier curves and the statistical comparison of the survival curves was performed by log-rank test. The univariate Cox proportional hazard modeling was used to examine factors related to survival. The proportional hazard assumption was tested using the Schoenfeld residuals. All tests were two sided with the significant level of 0.05. Statistical analysis was performed using the statistical platform R (version 3.4.1).

Results

Twenty-nine patients (43.9%) were female. Mean age at onset ± SD was 56.4 years (± 7.3). The median interval between symptoms onset and first visit at our clinic was 3 years (95% C.I. 2–4). The median follow-up from onset was 11 years (range 0–19). At the time of data collection 49 patients reached the phase 3 after a median time of 5 years (95% C. I. 4–6); thirty-two patients were confined to wheelchair after a median time of 7 years (95% C. I. 7–8); twenty-seven patients were deceased after a median time of 9 years (95% C. I. 8–10) (Fig. 1). The reported causes of death were pneumonia, tumors, cachexia, sudden death and cardiovascular.

At the last visit, the most frequent clinical findings in our cohort beside ataxia were as follows: dysarthria (92%), urinary incontinence (88%), erectile dysfunction (85%), dysphagia (78%), REM behavior disorder (75%), increased tendon jerks (74%), tremor (all types; 63%), rigidity (63%),

Table 1 Predictors of survival from the Cox proportional hazard model

	Phase 3		Phase 4		Death	
Predictors	HR [95% C.I.]	*p* value	HR [95% C.I.]	*p* value	HR [95% C.I.]	*p* value
Gender, male	0.94 [0.53 to 1.66]	0.826	1.24 [0.61 to 2.5]	0.55	0.96 [0.44 to 2.09]	0.923
Age at onset	*1.07* [*1.03* to *1.11*]	*0.001*	1.05 [1 to 1.1]	0.059	1.04 [0.99 to 1.09]	0.112
UMSARS	*1.04* [*1.02* to *1.06*]	*0.001*	*1.03* [*1.01* to *1.06*]	*0.021*	1.01 [0.98 to 1.04]	0.528
Nystagmus	2.13 [0.64 to 7.11]	0.221	3.18 [0.41 to 24.42]	0.267	1.61 [0.21 to 12.27]	0.647
Dysarthria	1.34 [0.67 to 2.67]	0.401	0.96 [0.44 to 2.11]	0.927	1.52 [0.6 to 3.88]	0.380
Tremor	1.25 [0.67 to 2.32]	0.479	0.87 [0.41 to 1.85]	0.722	1.08 [0.46 to 2.5]	0.862
Bradykinesia	1.55 [0.79 to 3.01]	0.199	1.47 [0.63 to 3.41]	0.374	0.94 [0.34 to 2.59]	0.904
Rigidity	*1.99* [*1.08* to *3.65*]	*0.027*	1.78 [0.86 to 3.68]	0.120	1.26 [0.54 to 2.93]	0.586
Increased knee jerks	0.75 [0.36 to 1.56]	0.440	0.75 [0.34 to 1.67]	0.484	0.7 [0.29 to 1.67]	0.418
Increased tone LL[a]	1.77 [0.63 to 4.97]	0.281	1.52 [0.52 to 4.4]	0.444	2.69 [0.96 to 7.52]	0.059
Babinski signs	2.32 [0.81 to 6.62]	0.115	1.37 [0.32 to 5.87]	0.675	1.49 [0.34 to 6.45]	0.593
Urinary Incontinence	1 [0.54 to 1.83]	0.995	0.75 [0.36 to 1.57]	0.441	0.88 [0.38 to 2.03]	0.759
Orthostatic hypotension	1.08 [0.54 to 2.13]	0.835	1.04 [0.44 to 2.43]	0.934	1.16 [0.43 to 3.15]	0.772
Syncope	1.19 [0.36 to 3.97]	0.778	0.53 [0.07 to 4.01]	0.537	0.66 [0.09 to 4.98]	0.685
Erectile dysfunction	1.25 [0.39 to 4.03]	0.709	1.21 [0.24 to 6.13]	0.819	0.58 [0.1 to 3.56]	0.561
Dysphagia	0.69 [0.38 to 1.27]	0.236	0.96 [0.47 to 1.97]	0.914	0.98 [0.41 to 2.32]	0.964
Stridor	1.14 [0.34 to 3.81]	0.826	1.58 [0.46 to 5.41]	0.469	n.a.	n.a.
RBD[a]	1.6 [0.78 to 3.26]	0.198	2.21 [0.82 to 5.96]	0.118	1.97 [0.7 to 5.52]	0.200
Cerebellar atrophy	1.86 [0.45 to 7.73]	0.396	2.32 [0.31 to 17.13]	0.410	1.51 [0.2 to 11.31]	0.690
Pons atrophy	1.71 [0.87 to 3.37]	0.118	1.4 [0.62 to 3.16]	0.416	2.71 [0.98 to 7.44]	0.054
HBS[a]	1.21 [0.65 to 2.26]	0.552	1.83 [0.81 to 4.11]	0.144	1.04 [0.44 to 2.47]	0.931
Putaminal rim	1.42 [0.55 to 3.66]	0.468	1.65 [0.56 to 4.82]	0.362	1.26 [0.29 to 5.47]	0.754

[a] *LL* lower limbs, *RBD* REM behavior disorder, *HBS* hot bun sign

bradykinesia (60%). Signs with lower occurrence were as follows: orthostatic hypotension (39%), stridor (33%), dystonia (30%), Babinski signs (21%), syncope (18%), nystagmus (11%), abnormal MMSE (11%) and increased tone at lower limbs (10%). Thirty percent of the patients were treated with L-Dopa. MRI scan detected constant cerebellar atrophy, pontine atrophy in 69%, hot cross bun sign in 58% and putamen rim hyperintensity in 15%. Finally, DaT-Scan usually performed at the beginning of the disease showed dopaminergic denervation in 87% of the tested patients.

As far as predictors are concerned a later onset age (HR 1.07; 95% C.I. 1.03–1.11; $p = 0.001$), a higher (UMSARS) score at first visit (HR 1.04; 95% C.I. 1.02–1.06; $p = 0.001$) and the presence of rigidity (HR 1.99; 95% C.I. 1.08–3.65; $p = 0.027$) predicted time to phase 3; a higher UMSARS score at first visit (HR 1.03; 95% C.I. 1.01–1.06; $p = 0.021$) predicted time to phase 4. No predictors were found for death (Table 1).

Discussion

We present the results of a retrospective center–based study of the predictors of survival and disability in MSA-C. The mean age at onset (56.4 years), the median disease duration to wheelchair (7 years) and to death (9 years) are in agreement with previous studies [4, 6–13] (Fig. 1). We sought for predictors of disease progression and we found an inverse correlation between age at onset and loss of independent walking (phase 3), and a direct correlation between UMSARS score, rigidity and this outcome that was not previously investigated. In addition, we found a direct correlation between UMSARS score and phase 4, and no significant predictor for death. Dysautonomia did not result as predictor of a faster progression as for instance in Coon et al. [18], Figueroa et al. [19], Low et al. [7] and Cao et al. [13] studies. The prospective European cohort study only found that incomplete bladder emptying predicted shorter survival [6]. A possible explanation is that in our study, we consider only occurrence of the autonomic features at the first visit in our clinic but not their severity or occurrence in the first years of the disease. We also found that UMSARS score at the first visit was a predictor of phase 3 and phase 4 but not of survival. Different patients and different numbers of patients available for these outcomes might be a possible explanation. On the other hand, the data from literature are conflicting. A recent metanalysis [5] found that early development of combined autonomic and motor features and early falls predicted survival. A higher UMSARS score was associated with poor survival by Cao et al. [13] but not by Low et al. [7]. Moreover, Figueroa et al. did not find early development of gait instability or aid requiring ambulation as predictor of shorter survival [19]. Finally, gender did not predict any outcome in our study. The effect of gender was negative in the metanalysis [5].

The occurrence of most clinical features was similar to those reported in other series of patients [6, 7] but the occurrence of nystagmus and orthostatic hypotension was lower and that of increased knee jerks higher in our series.

In our study, there are some weaknesses. The first concerns the limited number of patients enrolled in this study. However, it falls in the range of other prospective studies (54 in the European cohort [6] and 49 in the US cohort [7]) as well of other retrospective studies (21 in Shultz et al. [8], 31 in Tada et al. [10], 40 in Roncevic et al. [20], 17 in Figueroa et al. [19]). Secondly, retrospective data collection is a potential limitation, resulting in bias because of poor patients' recall. Indeed, some clinical data were obtained by the history recorded in the chart at the time of neurological examination. Nonetheless, retrospective studies are useful tools to evaluate rare disease for which prospective data collection are operatively difficult. Thirdly, the lack of pathologically confirmed cases. Nonetheless, we believe that our study may contribute to define the natural history of the less investigated phenotype of the multiple system atrophy in a Western population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

The study protocol was approved by local Ethics Committee of the Federico II University in Naples.

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