Title

Epidemiology of Multiple System Atrophy in Hokkaido, the Northernmost Island of Japan

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Abstract

Background: Multiple system atrophy (MSA) is an intractable neurodegenerative disorder that is characterized by various combinations of autonomic failure, cerebellar ataxia, and parkinsonism. We conducted an epidemiological study of MSA using the combined data of a national registry system and a postal survey in Hokkaido, Japan.

Methods: A postal survey was conducted on 2013 based on national registry data from 2006 to 2011. This survey contained the current status of each patient with MSA that had been collected from attending physicians and recorded into a national registry. Survey items included date, outcomes, primary symptoms, and activities of daily living at the last medical examination. Confirmation data of the diagnosis by a board-certified neurologist was also collected.

Results: Based on the national registry data, 1092 patients with MSA were selected as our target population. The response rate of the postal survey was 81% (885/1092). After excluding inappropriate responses, 839 patients with MSA were analyzed. Forty-nine percent of the patients were male, and the mean onset age was 62.1 ± 10.4 years. A Kaplan-Meier survival curve revealed that patients with onset symptoms of cerebellar ataxia had a better prognosis than those with onset of parkinsonism or autonomic failure ($p < 0.01$). Additionally, we found that a higher onset age was associated with poor prognosis.

Conclusions: We found that patients with cerebellar ataxia at onset had a better survival prognosis than those with parkinsonism or autonomic failure at onset, and that patients with an older age at onset had a worse survival prognosis.

Introduction

Multiple system atrophy (MSA) is a rare but devastating neurodegenerative disorder with a poor prognosis. The disease is characterized by symptoms of cerebellar ataxia, parkinsonism, and autonomic failure. Originally, patients with MSA were diagnosed into three different historical categories: striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA), or Shy-Drager syndrome (SDS). Pathologically, the overexpression of α-synuclein in the central nervous system, along with abnormal aggregation (as seen as glial cytoplasmic inclusion), was a common feature of the three categories; hence the concept of MSA was established [1]. According to the second consensus criteria, MSA has two phenotypes distinguished clinically based on predominant motor symptoms of either the cerebellar variant (MSA-C) or parkinsonism variant (MSA-P) [2]. In recent years, autonomic dysfunction as an onset symptom has been reconsidered as further understanding of MSA disease characteristics is required [3].

Some studies on the epidemiology of MSA have shown a regional difference in the frequency of MSA-C and MSA-P; MSA-C is more frequent in Japan than in Europe and the United States [4, 5]. This epidemiological difference has been confirmed by other studies in each region [6, 7]. The difference between MSA-C and MSA-P is the rate of motor symptom progression [8]. Additionally, a recent large cohort study reported that MSA-C has a better prognosis in terms of survival compared to MSA-P [7]. However, because of the rarity of the disease, variations in the natural history of MSA are still unclear because of the lack of community-based epidemiological studies.

In Japan, as well as in other countries, MSA is the most frequent disorder among

idiopathic spinocerebellar degenerative diseases [9]. The Ministry of Health, Labour and Welfare, Japan, has been managing a national registry system to support various intractable disorders including MSA and other hereditary/nonhereditary spinocerebellar degenerative diseases [10]. This national registry provides financial aid to individual patients to aid in the cost of medical expenses; thus, almost all patients with MSA are actively registered. Moreover, the registry contains information about patient diagnosis, but does not have information concerning the outcome of terminal stages of the disease.

Recent publications have reported genetic predispositions, including COQ2, to MSA [11]. Further investigation for the association between risk factors and disease characteristics is expected. In addition, new drug development for MSA is long overdue. Therefore, we aimed to conduct a cross-sectional study consisting of national registry data and postal surveys to address the natural history and characteristics of MSA on a community-based level.

Methods

Study design and subjects

This study was the first survey of the Hokkaido Rare Disease Consortium for MSA (HoRC-MSA), which is a project that was launched to construct a community-based prospective cohort study of MSA. This study was conducted as a retrospective cohort study using patient data from the national registry and surveys from the attending physicians (including neurologists) of each patient. According to the criteria established by the Research Committee of Ataxic Disease and the Ministry of Health, Labour and Welfare of Japan [10], the diagnosis of MSA in this registry system was based on

predominant manifestations from the beginning of the disorder. These manifestations were then used to classify the disease as parkinsonism onset type (SND), ataxia onset type (OPCA), or dysautonomia onset type (SDS) and was clinically diagnosed using the following criterion. Parkinsonism onset type had to start with parkinsonism in middle-aged individuals or later, and showed poor response to Parkinson's disease medications. Moreover, parkinsonism had to have been followed by cerebellar ataxia and autonomic failure. Ataxia onset type, on the other hand, had to start with cerebellar ataxia and develop in middle-aged individuals or later. Cerebellar ataxia then had to be followed by parkinsonism and autonomic failure. Finally, dysautonomia onset type had to start with autonomic failure including orthostatic hypotension, urinary disturbances, or impotence. These symptoms had to then be followed by parkinsonism and cerebellar ataxia more than one year later. On enrollment to the national registry, application documents, signs, and symptoms were recorded by attending physicians, and magnetic resonance images were reviewed by an expert neurologist with experience in the clinical practice of MSA. In addition, patients whose who were less than 30 years old at disease onset were excluded in analyses of survival and symptoms according to the second consensus criteria [12].

This study was conducted in Hokkaido, one of the four major islands located in Northern Japan. Hokkaido is the second largest island with a population of 5.5 million and, at the time of this study, 167 board-certified neurologists. Hokkaido is separated by the sea from Honshu, the main island of Japan; therefore, almost all of the patients with MSA had their attending physicians within Hokkaido. We studied patients with MSA registered in the national registry from 2006 to 2011. On February 2013, we conducted

a postal survey to the attending physician of each patient with MSA. This study was approved by the Institutional Review Board of Hokkaido University Hospital.

National registry system

From the national registry data, this study used patient demographics that included sex, date of birth, onset date, onset of symptoms, and date of first medical visit due to MSA symptoms. Onset symptoms were recorded by selecting cerebellar ataxia, parkinsonism, autonomic failure, or other symptoms in the application document. Data were then electronically recorded into the national registry database.

Postal survey

The target of the postal survey in this study was the latest attending physician of each patient with MSA. Surveys were filled out based on the latest data of each patient and included the date of death. The postal survey collected the latest doctor visit date of each patient, patient condition at the last doctor visit, predominant symptoms at the last doctor visit, unified MSA rating scale part 4 (UMSARS; 1: Completely independent to 5: Totally dependent and helpless, bedridden) at the last doctor visit, and confirmation of the diagnosis of MSA throughout the course of the disorder by board-certified neurologists. Our postal survey was a piece of paper that was kept simple and that was easy to answer. To enhance the response rate of this study, we announced the importance of this study before the survey, and sent a reminder letter to the attending physicians before the survey deadline.

Statistical analysis

Descriptive summaries were indicated by mean and SD for continuous variables, and frequencies and percentages were used for categorical variables. Survival from

symptom onset was calculated using the Kaplan-Meier analysis. The log-rank test and Cox regression analysis were used in uni- and multi-variate analyses, respectively. The significance level was set at $p < 0.05$. All statistical analyses were conducted with STATA version 12.0 (STATA Corporation, College Station, TX, USA).

Results

A total of 1092 patients with MSA were selected from the national registry database for this survey. The postal survey returned 885 cases (81%), including 839 MSA cases and 46 cases who reported an incorrect diagnosis of MSA (as judged by the current attending physician or board-certified neurologist) (Fig. 1). Patient demographics are shown in Table 1. Females comprised of 50.8% (426 cases) of the participants, and the mean age of onset was 62 years. The proportion of patients who were alive at the time of the survey was 46%, while 32% of the patients were deceased. The mean age of participants at last examination was 70. The proportion of patients who were diagnosed by board-certified neurologists at any time during the course of MSA was 89%. Demographics of patients alive at the time of the survey revealed that approximately 80% of them had lower activities of daily living (ADL) levels (grade 3 or more) in the UMSARS part 4 and that 62% of them had MSA-C. A Kaplan-Meier survival curve revealed that patients with onset symptoms of cerebellar ataxia (median 190 months, 95% confidence interval (CI) 163–236 months) had better a prognosis than those with onset symptoms of parkinsonism (median 147 months, 95% CI 103–275 months) or autonomic failure (median 134 months, 95% CI 105–188 months) ($p < 0.01$)(Fig. 2-A). Older age at onset was also associated with poor prognosis (Fig. 2-B). The association

between age at onset and onset symptoms showed that Parkinsonism onset increased with aging (Fig. 3-A). We also found that there was an association between sex and onset symptoms. Specifically, the proportion of males was higher in patients with autonomic failure onset than those with parkinsonism or cerebellar ataxia onset (Fig. 3-B). A multivariate analysis using a Cox proportional hazards model, adjusted by age at onset and sex, showed that patients with cerebellar ataxia or young age at onset had a good survival prognosis (Tab. 2).

Discussion

Our study, to the best of our knowledge, is the first large community-based retrospective cohort survey focused on the natural history of MSA. This study had three major findings. First, patients with cerebellar ataxia at onset exhibited a better survival prognosis. Second, patients with parkinsonism at onset were often older in age. Third, the proportion of patients with autonomic failure was larger in males than it was in females.

In this study, the MSA-C predominance in Japan that had been reported in previous studies was confirmed [5, 6]. On the other hand, some epidemiological reports from Europe and the United States have shown MSA-P predominance [13, 14]. The current study was community-based using a national registry database; thus, it was important that the previous finding of MSA-C predominance in Japan be confirmed in a community-based epidemiological study.

Our study showed poor survival prognosis for patients with higher ages at disease onset, and this result was consistent with that of previous studies [15, 16]. Our study

also showed an association between age of onset and onset symptoms. Some studies have reported no relationship between these two factors [7, 15]; however, other studies have shown that patients with MSA-P had an older age of onset than those with MSA-C [9, 17]. In addition, we found that onset with autonomic failure was more frequent in males than in females, and this result was also consistent with previous studies [9, 18]. One symptom of autonomic failure includes erectile impotency, which occurs only in men, and this difference may have influenced the proportion of male patients reported to have an onset of autonomic failure.

According to a previous study, the survival of patients with MSA is associated with their predominant symptoms (e.g. cerebellar ataxia in MSA-C and parkinsonism in MSA-P) [7]. In our study, this association was confirmed by differences found in the survival analysis based on onset symptoms. Other studies have reported that patients with autonomic failure at disease onset had worse prognoses than those that exhibited cerebellar ataxia at onset [19, 20]. In the current study, we found the same association even though the definition of autonomic failure in the national registry might be different from that in previous studies. Finally, the results of the Cox proportional hazards model showed that both older age at onset and parkinsonism at onset were independent risk factors of poor prognosis.

Some limitations of this study should be discussed. First, the validity of MSA diagnosis was a little inferior when compared to what has been used in studies that have employed the second consensus criteria [12]. However, experienced neurologists reviewed each application at the initial registration of patients with MSA. In addition, the majority of patients in this study were diagnosed by board-certified neurologists

throughout the course of their disease. Second, we were unable to factor in the outcomes of some of the patients because of a lack of patient follow-up or a failure of attending physicians to return the surveys. Therefore, the lack of information on these patients might have induced a certain amount of bias to this study. However, we were able to analyze approximately 80% of the total patients with MSA; hence, the results of our study should be considered reliable. Third, this was a retrospective cohort study based on national registry data, and we conducted this investigation by combining national registry data with a cross-sectional postal survey. Moreover, a large portion of this study was dependent on cooperation from the local neurologist community. Considering these limitations, it is possible that the results of our study could have some bias and lack information; however, its consistency with previous studies, along with the large sample size of patients with MSA, can provide significant insight into the epidemiological characteristics of patients with this disease.

Finally, the strength of this study is that this survey was based on national registry data and postal surveys. In MSA, exhaustive surveys using national registries are rare. Therefore, it is important that the results of previous studies are consistent with our results. Moreover, the number of patients included in our study was larger than what was included in previous investigations; thus, this study can reveal more information regarding the epidemiological aspects of MSA. In the future, prospective cohort studies based on our current report will be expected to reveal remaining issues such as cause of death, differences of dysautonomia history between MSA-C and MSA-P, and disease progression evaluated by various functional scales.

In conclusion, our findings confirmed that the onset symptoms of MSA varied with sex

and age. Moreover, patients with cerebellar ataxia at onset had a better survival prognosis than those with parkinsonism or autonomic failure at onset, while patients older in age at MSA onset had a worse survival prognosis.

Acknowledgments

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Conflict of interest:

None

Ethical approval:

For this type of study, formal consent is not required.

Table

Table 1. Subject demographics

	Subjects (n = 839)
Age	
Symptom onset	62.1 (10.4)
At survey (last examination)	70.3 (9.3)
Sex (Female)	426 (50.8)
Symptoms at onset	
Ataxia	522 (62.2)
Parkinsonism	186 (22.2)
Dysautonomia	73 (8.7)
Other/Mixed	58 (6.9)
Condition at survey	
Alive	382 (45.5)
Deceased	264 (31.5)
Doctor changed	150 (17.9)
Lost	23 (2.7)
Diagnostic certainty	
Neurologist diagnosed	746 (88.9)

Subject status (alive = 382)		
Dominant at survey		
Ataxia	238	(62.6)
Parkinsonism	90	(23.7)
Undistinguishable	52	(13.7)
UMSARS part 4 at survey (alive = 382)		
Completely independent	16	(4.2)
Not completely independent	64	(16.8)
More dependent	58	(15.2)
Very dependent	99	(26.0)
Totally dependent and helpless	144	(37.8)

Age: mean (SD), Others: Number (% in total)

Table 2. Crude and adjusted hazard ratios, along with 95% confidence intervals (CI) for factors associated with survival

	Crude			Adjusted		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Onset						
Ataxia	1.00	–		1.00	–	
Parkinsonism	1.84	1.35–2.52	<0.001	1.69	1.23–2.32	0.001
Dysautonomia	1.66	1.09–2.53	0.018	1.50	0.98–2.30	0.064
Onset age						
Under 50	1.00	–		1.00	–	
50s	2.05	1.23–3.43	0.006	1.82	1.08–3.05	0.024
60s	2.99	1.82–4.89	<0.001	2.51	1.52–4.14	<0.001
70s	4.72	2.74–8.12	<0.001	3.49	1.99–6.14	<0.001
80 or more	14.03	6.66–29.56	<0.001	10.57	4.88–22.9	<0.001
Sex						
Female	1.00	–		1.00	–	
Male	1.28	1.00–1.64	0.054	1.31	0.99–1.72	0.051

Figures

Figure 1

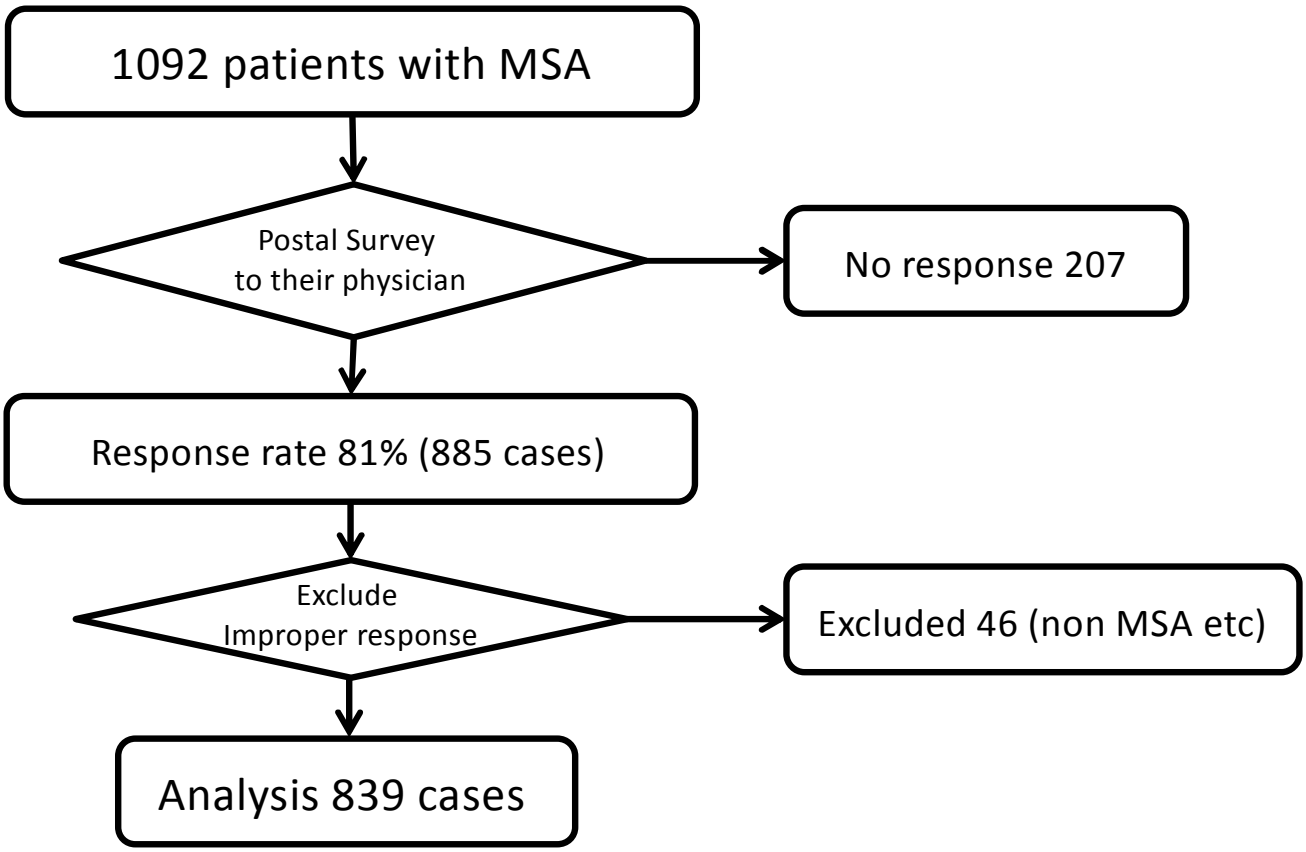
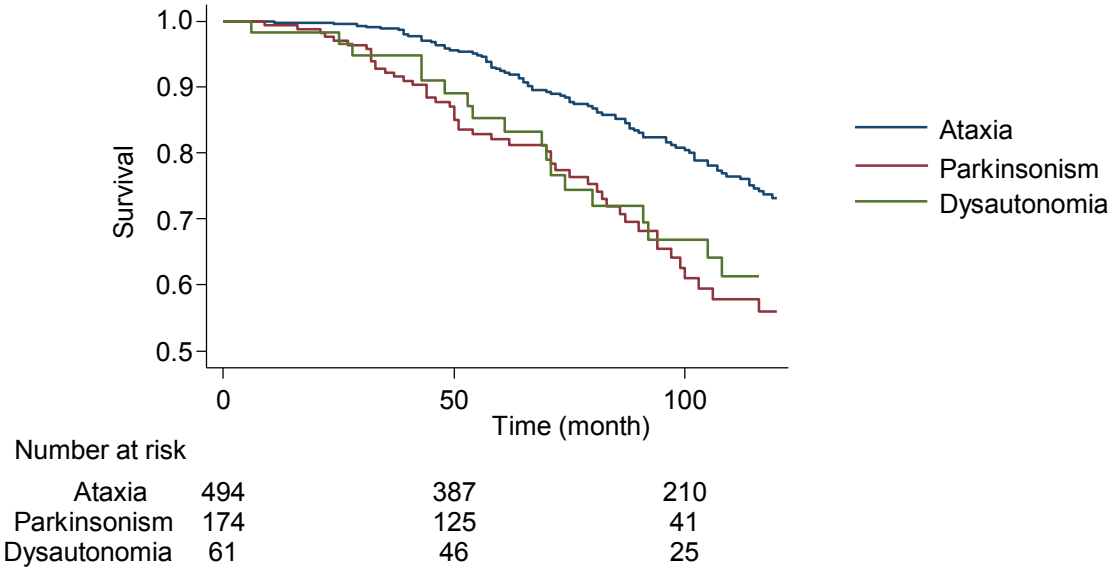


Figure 2.

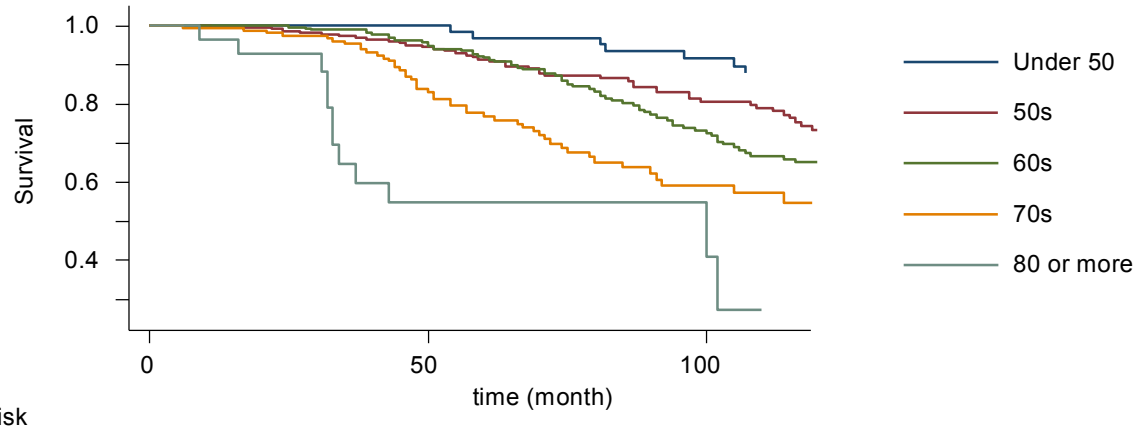
(a)



Number at risk

Ataxia	494	387	210
Parkinsonism	174	125	41
Dysautonomia	61	46	25

(b)

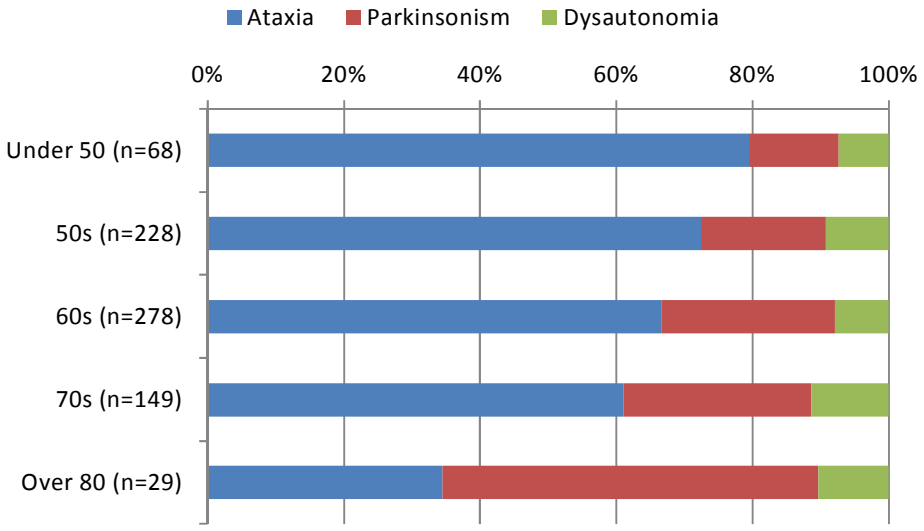


Number at risk

Under 50	68	64	47
50s	236	189	106
60s	288	226	102
70s	163	103	35
80 or more	28	9	4

Figure 3.

(a)


Ataxia
Parkinsonism
Dysautonomia
0%
20%
40%
60%
80%
100%
Under 50 (n=68)
50s (n=228)
60s (n=278)
70s (n=149)
Over 80 (n=29)

(b)

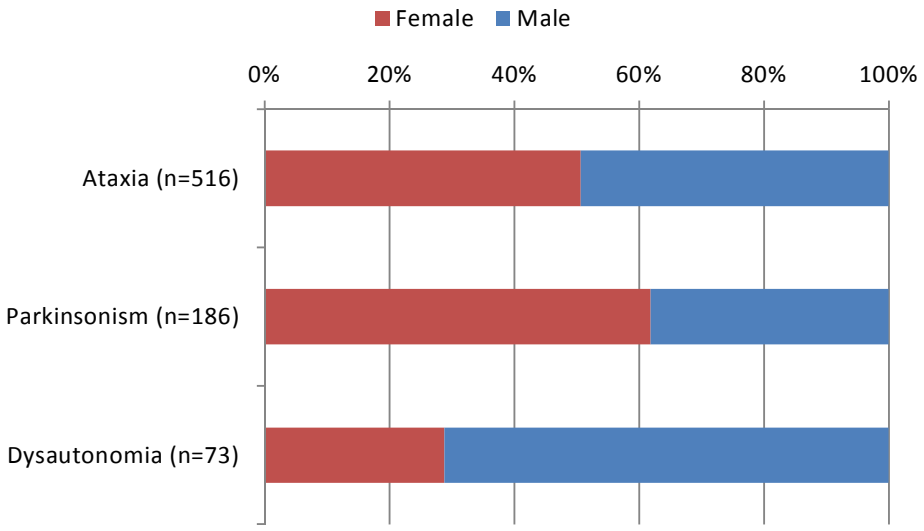

Female
Male
0%
20%
40%
60%
80%
100%
Ataxia (n=516)
Parkinsonism (n=186)
Dysautonomia (n=73)

Figure Legends

Figure 1

Study flow diagram

Figure 2

Kaplan-Meier survival plot

(a) Survival analysis stratified by onset symptom

(b) Survival analysis stratified by onset age

Figure 3

Association between onset symptoms and onset age/sex

(a) onset age and onset symptoms

(b) sex and onset symptoms

1. Quinn N. Multiple system atrophy--the nature of the beast. J Neurol Neurosurg Psychiatry. 1989;Suppl.(78-89.
2. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci. 1999;163(1):94-98.
3. Colosimo C. Nonmotor presentations of multiple system atrophy. Nat Rev Neurol. 2011;7(5):295-298.
4. Kollensperger M, Geser F, Ndayisaba JP, Boesch S, Seppi K, Ostergaard K, et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. Mov Disord. 2010;25(15):2604-2612.
5. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain. 2002;125(Pt 5):1070-1083.
6. Yabe I, Soma H, Takei A, Fujiki N, Yanagihara T, Sasaki H. MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA. J Neurol Sci. 2006;249(2):115-121.
7. Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, et al. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013;12(3):264-274.
8. Geser F, Seppi K, Stampfer-Kountchev M, Kollensperger M, Diem A, Ndayisaba JP, et al. The European Multiple System Atrophy-Study Group (EMSA-SG). J Neural Transm. 2005;112(12):1677-1686.
9. Hirayama K, Takayanagi T, Nakamura R, Yanagisawa N, Hattori T, Kita K, et al. Spinocerebellar degenerations in Japan: a nationwide epidemiological and clinical study. Acta Neurol Scand Suppl. 1994;153(1-22.
10. Tsuji S, Onodera O, Goto J, Nishizawa M. Sporadic ataxias in Japan--a population-based epidemiological study. Cerebellum. 2008;7(2):189-197.
11. Collaboration TM-SAR. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med. 2013;369(3):233-244.
12. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008;71(9):670-676.

13. Wenning GK, Ben-Shlomo Y, Hughes A, Daniel SE, Lees A, Quinn NP. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000;68(4):434-440.
14. Chrysostome V, Tison F, Yekhlef F, Sourgen C, Baldi I, Dartigues JF. Epidemiology of multiple system atrophy: a prevalence and pilot risk factor study in Aquitaine, France. Neuroepidemiology. 2004;23(4):201-208.
15. Testa D, Filippini G, Farinotti M, Palazzini E, Caraceni T. Survival in multiple system atrophy: a study of prognostic factors in 59 cases. J Neurol. 1996;243(5):401-404.
16. Figueroa JJ, Singer W, Parsaik A, Benarroch EE, Ahlskog JE, Fealey RD, et al. Multiple system atrophy: Prognostic indicators of survival. Mov Disord. 2014;29(9):1151-1157.
17. Wullner U, Schmitz-Hubsch T, Abele M, Antony G, Bauer P, Eggert K. Features of probable multiple system atrophy patients identified among 4770 patients with parkinsonism enrolled in the multicentre registry of the German Competence Network on Parkinson's disease. J Neural Transm. 2007;114(9):1161-1165.
18. Hirayama K, Kita K. [Clinical features of "multiple system atrophies"--olivo-ponto-cerebellar atrophy, striato-nigral degeneration and Shy-Drager syndrome]. Rinsho Shinkeigaku. 1985;25(10):1196-1203.
19. O'Sullivan SS, Massey LA, Williams DR, Silveira-Moriyama L, Kempster PA, Holton JL, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain. 2008;131(Pt 5):1362-1372.
20. Tada M, Onodera O, Ozawa T, Piao YS, Kakita A, Takahashi H, et al. Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. Arch Neurol. 2007;64(2):256-260.