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The Japan MSA registry: A multicenter cohort study of multiple system atrophy

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Abstract

Background: Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure and various motor symptoms. While MSA-C (cerebellar type) predominates in East Asia, MSA-P (parkinsonian type) predominates in Europe and North America. This nationwide patient registry aimed to (1) conduct a prospective natural history study of MSA in Japan, (2) facilitate patient recruitment for clinical trials, and (3) deposit bioresources and clinical information in a biobank.

Methods: Thirteen institutions participated in this study. Clinical information was obtained by neurologists from the patients visiting the hospital every 12 months to assess the UMSARS Part 2 scores and by telephone interviews by nurses every 6 months to assess UMSARS Part 1 scores and to determine whether clinical events had occurred.

Results: Demographic data from 329 MSA patients (216 MSA-C and 113 MSA-P) were analyzed. The mean age at symptom onset was 58.2 years (standard deviation, 8.9); the mean duration of symptoms at enrollment was 3.5 years (standard deviation, 2.2). The mean 12-month changes in the UMSARS Part 1 and Part 2 scores were 7.9 (standard deviation, 5.6) and 6.4 (standard deviation, 5.9), respectively. The patient registry proved useful in recruiting participants for clinical trials, including those with gene variants. Clinical information and biospecimens were deposited in a biobank.

For affiliations refer to page 276.

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Discussion: The study highlighted the importance of telephone interviews in minimizing drop-out rates in natural history studies and demonstrated similar MSA progression rates across populations. The deposited bioresources are available to researchers upon request, aiming to contribute to future MSA researches.

KEYWORDS
multicenter cohort study, multiple system atrophy, natural history, patient registry

1 | INTRODUCTION

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized clinically by autonomic failure with various combinations of parkinsonism, cerebellar ataxia, and pyramidal signs, and neuropathologically by oligodendroglial cytoplasmic inclusions of α-synuclein and neuronal loss. On the basis of the predominant motor phenotype, MSA has been classified into two clinical subtypes: the parkinsonian type (MSA-P) and the cerebellar type (MSA-C).[1] The prevalence of MSA has been reported to be 9.3 cases per 100,000 population in Japan.[2] Intriguingly, MSA-C predominates MSA-P in East Asia including Japan,[3,4] China,[5] and Korea,[6] whereas MSA-P is more frequent in Europe and North America.[7,8] Recent meta-analyses revealed that the V393A variant in *COQ2*, which is relatively common in East Asia but almost absent in Europe, is especially associated with the MSA-C subtype,[9,10] but many genetic and environmental factors underlying MSA still remain to be elucidated.

Whereas large-scale prospective studies of the natural history of MSA have been reported mainly in Europe and North America,[7,8] the only report from East Asia, where the predominant subtype is different, is from Hokkaido, the northernmost island of Japan.[4] Thus, it is crucial to establish a nationwide patient registry and conduct prospective natural history studies of MSA patients throughout Japan. We have three primary objectives in this patient registry: (1) to conduct studies of the natural history of MSA in the Japanese population by prospectively observing changes in the clinical rating scales and the occurrence of clinical events; (2) to facilitate the recruitment of patients to clinical trials; and (3) to deposit bioresource and clinical information in a biobank and make them available to the research community.

We herein describe the establishment of the MSA registry in Japan and the clinical and epidemiological data of MSA patients including the changes in rating scales in one year that were provided by 13 institutions across Japan to the MSA registry.

2 | METHODS

2.1 | Japan MSA registry

The framework of the MSA patient registry is shown in Figure 1. Patients who meet the second consensus statement on the diagnostic criteria of possible or probable MSA are enrolled.[11] In this registry, physicians at participating institutions enroll MSA patients. The purpose of the registry, including the prospective collection of clinical information and the deposit of bioresource and clinical information into a public research resource bank, is fully explained to the patients, after which written informed consent is obtained from the participants. The prospective collection of clinical information is assessed by nurses through telephone interviews every 6 months and by neurologists every 12 months. A contract research organization (BELLSYSTEM24 Holdings, Inc.), which has signed a nondisclosure agreement with each institution, is in charge of data management. The personal and clinical information thus obtained is kept in a database on the cloud that fulfills the Electronic Records/Electronic

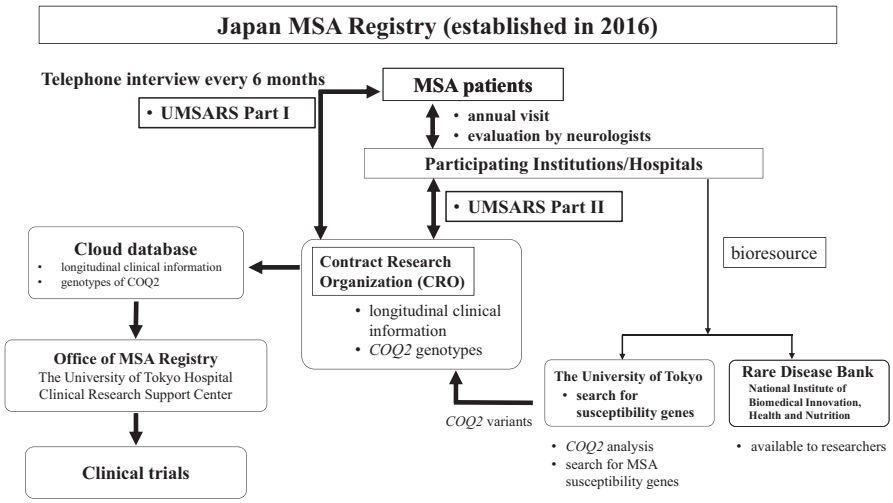

FIGURE 1 Framework of the Japan MSA registry. This figure illustrates the process of data and bioresource collection in this registry system. Physicians enroll multiple system atrophy (MSA) patients, and the personal and clinical information obtained is stored in a cloud database. The collected bioresources are kept at the University of Tokyo and, simultaneously, deposited to the National Institute of Biomedical Innovation, Health and Nutrition (NIBIHN). UMSARS, unified MSA rating scale.

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Signature (ER/ES) guidelines. Thirteen institutions across Japan participated in this study and began enrolling patients in August 2016 after receiving approval from the Institutional Review Boards of the participating institutions.

2.2 | Evaluations

The Japanese version of Unified Multiple System Atrophy Rating Scale (UMSARS) Part 1 and Part 2 scores, which have been validated for their reliability and validity, were used for the assessment of the clinical severity of MSA in this study.[12,13] Clinical information was obtained by neurologists from the patients visiting the hospital every 12 months to assess the UMSARS Part 2 scores and by telephone interviews by nurses every 6 months to assess UMSARS Part 1 scores and to further inquire whether and when clinical events (gastrostomy, inability to ambulate even with assistance, introduction of a bladder catheter, noninvasive positive pressure ventilation, tracheostomy, ventilator, and death) had occurred.

2.3 | Data collection and analysis

Hardcopies of case report forms were sent to the contract research organization for data entry, where they were checked for any missing or unusual values and any necessary queries were communicated with the participating neurologists who had previously registered the data. Data were entered into the cloud database (Hitachi, Ltd.). In this study, the data were downloaded from the database and analyzed using Microsoft Excel 2013 and R (version 3.4.1).

2.4 | Role of the funding source

Funds from the Japan Agency for Medical Research and Development (AMED), MEXT KAKENHI, and Nobelpharma Co., Ltd. supported the study. The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

3 | RESULTS

3.1 | Demographic data

As of May 2020, 329 MSA patients had been enrolled in the study for more than 12 months. The demographic data are summarized in Table 1. Of the 329 patients, 170 (51.7%) were men and 159 (48.3%) were women. The mean age at symptom onset was 58.2 years

TABLE 1 Demographic data of the MSA patients in the MSA registry from August 2016 to May 2019.

	Overall	MSA-C	MSA-P
Number (%)	329 (100)	216 (65.7)	113 (34.3)
Diagnostic criteria			
Possible, *n* (%)	123 (37.4)	80 (37.0)	43 (38.1)
Probable, *n* (%)	206 (62.6)	136 (63.0)	70 (61.9)
Sex			
Women, *n* (%)	159 (48.3)	94 (43.5)	65 (57.5)
Men, *n* (%)	170 (51.7)	122 (56.5)	48 (42.5)
Age			
Study entry, years (mean [SD])	61.6 [8.9]	60.1 [8.7]	63.5 [8.8]
Symptom onset, years (mean [SD])	58.2 [8.9]	57.2 [8.5]	60.1 [9.2]
Duration of symptoms at entry, years (mean [SD])	3.5 [2.2]	3.5 [2.3]	3.4 [2.1]
Symptoms at entry			
Urinary incontinence, *n* (%)	181 (55.0)	113 (52.3)	68 (60.2)
Orthostatic hypotension, *n* (%)	204 (62.0)	138 (63.9)	66 (58.4)
Incomplete bladder emptying, *n* (%)	186 (56.5)	116 (53.7)	70 (61.9)
Rapidly progressive parkinsonism, *n* (%)	104 (31.6)	19 (8.8)	85 (75.2)
Beneficial response to levodopa, *n* (%)	Not applicable	Not applicable	5 (4.7)
Cerebellar symptoms, *n* (%)	287 (87.2)	216 (100)	71 (62.8)
Babinski sign, *n* (%)	94 (28.6)	54 (25.0)	40 (35.4)
Impotence of men, *n* (%)	143 (84.1)	103 (84.4)	40 (83.3)

Note: Orthostatic hypotension is defined as a fall in systolic blood pressure of ≥30 mm Hg or diastolic blood pressure of ≥15 mm Hg, within 3 min of standing.

Abbreviations: *n*, number; SD, standard deviation.

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[standard deviation (SD), 8.9]; the mean duration of symptoms at entry was 3.5 years (SD, 2.2). These findings were not significantly different between MSA-C and MSA-P patients. On the basis of the second consensus criteria, 113 (34.3%) of the patients were classified as having MSA-P and 216 (65.7%) as having MSA-C, and 123 patients (37.4%) were classified as having possible MSA (possible MSA-P, 35.0%; possible MSA-C, 65.0%) and 206 (62.6%) as having probable MSA (probable MSA-P, 34.0%; probable MSA-C, 66.0%). At entry, 71 (62.8%) patients with MSA-P had cerebellar symptoms and 104 (31.6%) patients with MSA-C showed parkinsonism. Urinary symptoms [272 patients (82.7%)] including urinary incontinence (181 [55.0%]), incomplete bladder emptying (186 [56.5%]), and urinary urgency (227 [69.0%]) were more common than orthostatic hypotension (204 [62.0%]).

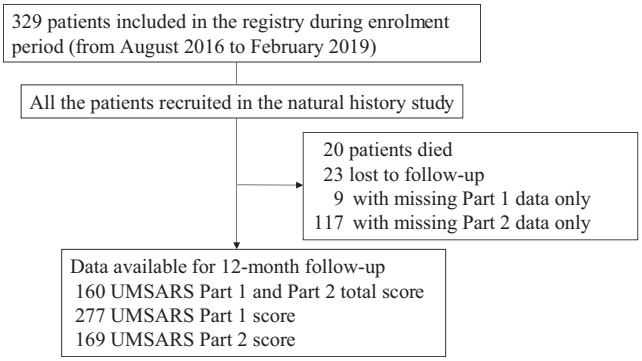

FIGURE 2 Study flow diagram: 12-month follow-up of 329 patients. In this cohort study, 329 participants were registered from August 2016 to February 2019. During the first 12 months of enrollment, 20 participants died and 23 were lost to follow-up. We were unable to obtain Part 1 data from 9 participants and Part 2 data from 117 participants. UMSARS, unified MSA rating scale.

3.2 | Recruitment into clinical trials

For our recent clinical trial, "Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of MSA-01 in Patients with Multiple System Atrophy (UMIN000031771)," we began recruiting patients in June 2018 and achieved its planned primary enrollment of 140 MSA patients by May 2019.[14] This clinical trial was planned to enroll more than 20 patients with *COQ2* variants, and the prior genetic analysis of MSA patients enrolled in the registry enabled efficient recruitment of patients with *COQ2* variants. In addition, since MSA patients attending facilities other than those participating in this clinical trial had been smoothly enrolled in the registry, we were able to inform them of the clinical trial, rapidly allowing for large-scale screening in a short period of time. The registry proved to be very useful in recruiting patients with rare diseases in a short period of time, particularly in recruiting patients carrying rare gene variants.

3.3 | Change in the UMSARS score over 12 months

The drop-out rates of the patients for acquisition of the Part 1 and Part 2 scores at one year were 15.8% and 48.6%, respectively. During the one-year follow-up, 20 of the 329 patients died (Figure 2). The mean 12-month change in the UMSARS Part 1 score was 7.9 [SD 5.6], and that in the UMSARS Part 2 score was 6.4 [SD 5.9] (Table 2).

3.4 | Deposit to the Biobank

All clinical information excluding personal identifiable data and biospecimens including genomic DNA, plasma, and lymphoblastoid cell

TABLE 2 UMSARS score progression in 12 months.

	UMSARS total score (Part 1 and Part 2)	UMSARS Part 1 score	UMSARS Part 2 score
Baseline score			
Number	329	329	329
Mean (SD)	39.2 (16.8)	18.6 (8.3)	20.5 (9.1)
Median [Q1, Q3]	37 [27, 50]	17 [13, 23]	19 [13, 26]
95% CI	37.4–41.0	17.7–19.5	19.5–21.5
12-month follow-up score			
Number	160[a]	277	169
Mean (SD)	49.6 (16.6)	25.4 (8.7)	25.6 (9.1)
Median [Q1, Q3]	49.5 [38, 58]	25 [19, 30]	25 [19, 32]
95% CI	47.0–52.2	24.4–26.5	25.2–27.0
Change in score in 12 months			
Mean (SD)	13.0 (9.0)	7.9 (5.6)	6.4 (5.9)
Median [Q1, Q3]	12 [6, 18]	7 [3, 11]	6 [3, 9]
95% CI	11.6–14.4	7.2–8.5	5.5–7.3

Abbreviations: CI, confidence interval; Q1, the first quartile; Q3, the third quartile; SD, standard deviation.

[a]Number of patients with data available for both Part 1 and Part 2.

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lines are deposited to the Research Resource Bank for Intractable Diseases with the support of the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIHN) (https://www.nibiohn.go.jp/en/). Biospecimens are managed using barcodes and their quality is controlled under standard operating procedures. Clinical information is accessible only through dedicated biometrically authenticated terminals. These biospecimens are available for distribution in accordance with the regulations of the Research Resource Bank for Intractable Diseases.

4 | DISCUSSION

In our study, on the basis of the second consensus criteria, 65.7% of the patients were classified as having MSA-C and 34.3% as having MSA-P. In the previously reported study from Hokkaido University,[4] the distribution of disease subtypes was reported as 62.2% cerebellar-dominant, 22.2% parkinsonism-dominant, 8.7% autonomic dysfunction-dominant, and 6.9% other or unclassifiable. In a study from Nagoya University[3] 67.4% were classified as MSA-C and 32.6% as MSA-P. In a research consortium study predating our registry[15] 71.3% were classified as MSA-C and 23.4% as MSA-P. Taken together, the frequency of disease subtypes in Japan is generally observed to be around 60–70% as MSA-C and 25–35% as MSA-P, consistent with our findings in this study.

In prospective natural history studies, it is essential to minimize the drop-out rate. In the acquisition of UMSARS Part 1 scores, the drop-out rate was found to be 15.8% at one year, which is much lower than the drop-out rate in the acquisition of UMSARS Part 2 scores (48.6% at one year). Drop-out rates, including deaths, loss to follow-up, and loss to evaluate, after one year in the two previous prospective natural history studies based on assessments at hospital visits were reported as 50.4 and 45.1% for Part 1 and 25.0% and 54.9% for Part 2 (Table 3).[7,8] Other than drop-out due to death, rapidly progressive motor disturbances in MSA patients often makes it difficult for them to attend study visits even after one year. Therefore, we believe that the drop-out rate in Part 1 based on the nurse's telephone interview was substantially lower than the drop-out rate in Part 2 based on the neurologist's examination at the hospital visit. The development of a reliable, validated, and telemedically assessable clinical scale would be

TABLE 3 Comparison of the present study with previous studies.

	Present study	European study[a]	North American study
Diagnostic criteria[11] (Possible, *n*/Probable, *n*)	123/206	32/109	0/175
Sex (Female, *n*/Male, *n*)	159/170	62/79	70/105
Age			
Study entry, years (mean [SD])	61.6 [8.9]	62.1 [7.7]	63.4 [8.6]
Symptom onset, years (mean [SD])	58.2 [8.9]	56.2 [8.4]	not available
Duration of symptoms at entry, years (mean [SD])	3.5 [2.2]	5.5 [3.8]	not available
MSA-C, *n*/MSA-P, *n*	216/113	54/87	49/126
Number at baseline[b]			
UMSARS Part 1	329	125	175
UMSARS Part 2	329	124	175
Number at 12 months[b]			
UMSARS Part 1	277	62	96
UMSARS Part 2	169	58	79
Percentage reduction in the number of subjects assessed from baseline to 12 months (Part 1/Part 2)	15.8%/48.6%	50.4%/25.0%	45.1%/54.9%
Number of confirmed deaths in 12 months/Number at baseline	20/329 (6.1%)	20/125 (16.0%)	41/175 (23.4%)
Baseline score			
UMSARS Part 1 score, mean [SD]	18.6 [8.3]	25.2 [8.8]	25.0 [8.1]
UMSARS Part 2 score, mean [SD]	20.5 [9.1]	25.9 [9]	26.1 [9.3]
UMSARS total score, mean [SD]	39.2 [16.8]	51.2 [17]	51.1 [16.3]
Change from baseline at 12 months			
UMSARS Part 1 score, mean [SD]	7.9 [5.6]	6.5 [6]	3.9 [5.8]
UMSARS Part 2 score, mean [SD]	6.4 [5.9]	8.2 [7]	4.6 [5.0]
UMSARS total score, mean [SD]	13.0 [9.0]	14.6 [11.8]	7.6 [8.4]

Abbreviations: *n*, number; SD, standard deviation.

[a]In calculating the mean scores, some missing values were estimated and filled through linear interpolation.

[b]Number of subjects actually evaluated using the UMSARS.

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useful in large-scale, long-term natural history studies and clinical trials, especially in movement disorders, including MSA.

The mean 12-month differences in UMSARS Part 1 scores were reported to be 6.5 [SD 6] and 3.9 [SD 6] and the mean 12-month differences in the UMSARS Part 2 scores were reported to be 8.2 [SD 7] and 4.6 [SD 5] in Europe and North America, respectively[7,8] (Table 3). Low et al. attributed the differences in the reported changes in the UMSARS Part 1 and Part 2 scores at 12 months between the European and the North American studies to selection criteria, in which the North American study included both possible and probable MSA cases, while the European study included only probable MSA cases.[7] The differences between our study and the two previous studies include a higher frequency of MSA-C, shorter duration of illness, and lower baseline scores. In addition, our study had a much lower drop-out rate because the follow-up of the Part 1 score was conducted by telephone interview. These differences in the background of each study may be related to the changes in the UMSARS scores over a 12 month in each study and should be kept in mind when designing clinical trials.

The second consensus criteria[11] were used as the selection criteria in this registry. Recently, the new diagnostic criteria for MSA diagnosis were published in 2022,[1] in which the "Clinically Probable" category was developed to increase sensitivity while maintaining specificity and the "Possible Prodromal" category was developed to maximize sensitivity. These new diagnostic criteria are considered to be more sensitive than the previous criteria and would be therefore important for clarifying the natural history of early-stage cases. In the future, we would like to include the new diagnostic criteria in the Japan MSA registry to further expand the natural history study, especially for patients with early onset, keeping the second consensus criteria (Gilman) to maintain consistency in the natural history study.

The bioresources obtained in this study (genomic DNA, plasma, and lymphoblastoid cell lines) were deposited to the rare disease bank at the NIBIHN, which are made available to researchers upon request to NIBIHN. We hope the bioresources will contribute to various research studies on MSA.

Our registry aims to be utilized in post-marketing surveillance and beyond. Additionally, being ongoing since 2016, it is a long-term registry, and we intend to explore its application for demonstrating long-term efficacy in the future.

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REFERENCES

1. Wenning GK, Stankovic I, Vignatelli L, et al. The Movement Disorder Society criteria for the diagnosis of multiple system atrophy. *Mov Disord*. 2022;37:1131-1148.
2. Japan Intractable Diseases Information Center. https://www.nanbyou.or.jp/
3. Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: An analysis of 230 Japanese patients. *Brain*. 2002;125:1070-1083.
4. Sakushima K, Nishimoto N, Nojima M, et al. Epidemiology of multiple system atrophy in Hokkaido, the Northernmost Island of Japan. *Cerebellum*. 2015;14:682-687.
5. Zhang LY, Cao B, Zou Y, et al. Causes of death in Chinese patients with multiple system atrophy. *Aging Dis*. 2018;9:102-108.
6. Seo JH, Yong SW, Song SK, Lee JE, Sohn YH, Lee PH. A case-control study of multiple system atrophy in Korean patients. *Mov Disord*. 2010;25:1953-1959.
7. Low PA, Reich SG, Jankovic J, et al. Natural history of multiple system atrophy in the USA: a prospective cohort study. *Lancet Neurol*. 2015;14:710-719.
8. Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol*. 2013;12:264-274.
9. Porto KJ, Hirano M, Mitsui J, et al. COQ2 V393A confers high risk susceptibility for multiple system atrophy in east Asian population. *J Neurol Sci*. 2021;429:1-32.
10. Zhao QZ, Yang X, Tian SJ, An R, Zheng JH, Xu Y. Association of the COQ2 V393A variant with risk of multiple system atrophy in east Asians: a case–control study and meta-analysis of the literature. *Neurol Sci*. 2016;37:423-430.
11. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71:670-676.
12. Wenning GK, Tison F, Seppi K, et al. Development and validation of the unified multiple system atrophy rating scale (UMSARS). *Mov Disord*. 2004;19:1391-1402.
13. Chikada A, Mitsui J, Matsukawa T, et al. Reliability and validity of Japanese version of unified multiple system atrophy rating scale. *Neurol Clin Neurosci*. 2021;9:171-180.
14. Mitsui J, Matsukawa T, Uemura Y, et al. High-dose ubiquinol supplementation in multiple-system atrophy: a multicentre, randomised, double-blinded, placebo-controlled phase 2 trial. *eClinicalMedicine*. 2023;59:101920.
15. Multiple-System Atrophy Research Collaboration. Mutations in COQ2 in familial and sporadic multiple-system atrophy. *N Engl J Med*. 2013;369:233-244.

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