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【 ORIGINAL ARTICLE 】

# The Movement Disorder Society Criteria: Its Clinical Usefulness in Multiple System Atrophy

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**Abstract:**

**Objective** In 2022, Wenning et al. proposed the Movement Disorder Society Criteria (MDS criteria) for the Diagnosis of Multiple System Atrophy (MSA). These criteria were expected to provide useful alternatives to the second consensus statement. We examined trends in these diagnostic criteria.

**Methods** We used patient data registered with the Hokkaido Rare Disease Consortium for Multiple System Atrophy, which has been recruiting patients with MSA through medical facilities in Hokkaido since November 2014. Patients were evaluated according to the MDS criteria based on neurological examinations and imaging findings at three separate times: the first evaluation, the time of enrollment (diagnosis), and the most recent evaluation (final evaluation).

**Results** The MDS criteria were examined in 68 of 244 patients enrolled between November 2014 and July 2022. At the initial evaluation, the classifications were as follows: clinically established (n=27; 39.7%); clinically probable (n=13; 19.1%); possible prodromal (n=12; 17.6%); and negative [did not meet criteria (n=16; 23.5%)]. At the time of diagnosis, the classifications were as follows: clinically established (n=45; 66.2%); clinically probable (n=12; 17.6%); possible prodromal (n=4; 5.9%); and negative (n=7; 10.3%). At the final evaluation, the classifications were as follows: clinically established (n=52; 76.5%); clinically probable (n=9; 13.2%); possible prodromal (n=2; 2.9%); and negative (n=5; 7.4%).

**Conclusion** We were able to clarify the changes in the criteria values and transition of patients due to the clarification of imaging and supportive findings in the MDS criteria.

**Key words:** multiple system atrophy, the Movement Disorder Society Criteria, second consensus statement, usefulness, utility, clinical assessment

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## Introduction

Multiple system atrophy (MSA) is an adult-onset progressive neurodegenerative disease characterized by autonomic dysfunction, parkinsonism, and ataxia. Patients usually require wheelchairs within 5 years and often die within 6-10 years of the disease onset, with few patients surviving for more than 15 years (1). While the pathogenesis of MSA has been revealed, including α-synuclein aggregation, tubulin

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**Table 1. Second Consensus Statement (7).**

| | Probable MSA | Possible MSA |
|---|---|---|
| Criteria | A sporadic, progressive, adult (>30y)-onset disease characterized by | |
| | ・Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3min of standing by at least 30 mmHg systolic or 15 mmHg diastolic<br>and<br>・Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability)<br>or<br>・A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction | ・Parkinsonism (bradykinesia with rigidity, tremor, or postural instability)<br>or<br>・A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)<br>and<br>・At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA)<br>and<br>・At least one of the additional features |
| Additional features | Possible MSA-P or MSA-C<br>・Babinski sign with hyperreflexia<br>・Stridor<br>Possible MSA-P<br>・Rapidly progressive parkinsonism<br>・Poor response to levodopa<br>・Postural instability within 3y of motor onset<br>・Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction<br>・Dysphagia within 5y of motor onset<br>・Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum<br>・Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum<br>Possible MSA-C<br>・Parkinsonism (bradykinesia and rigidity)<br>・Atrophy on MRI of putamen, middle cerebellar peduncle, or pons<br>・Hypometabolism on FDG-PET in putamen<br>・Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET | |
| Features supporting (red flags) and not supporting a diagnosis of MSA | Supporting features<br>・Orofacial dystonia<br>・Disproportionate antecollis<br>・Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)<br>・Contractures of hands or feet<br>・Inspiratory sighs<br>・Severe dysphonia<br>・Severe dysarthria sclerosis<br>・New or increased snoring<br>・Cold hands and feet<br>・Pathologic laughter or crying<br>・Jerky, myoclonic postural/action tremor | Nonsupporting features<br>・Classic pill-rolling rest tremor<br>・Clinically significant neuropathy<br>・Hallucinations not induced by drugs<br>・Onset after age 75 years old<br>・Family history of ataxia or parkinsonism<br>・Dementia (on DSM-IV)<br>・White matter lesions suggesting multiple |

MSA: multiple system atrophy, MSA-C: MSA cerebellar dominant type, MSA-P: MSA parkinsonian dominant type, MRI: magnetic resonance imaging, FDG-PET: fluorodeoxyglucose-positron emission tomography, SPECT: single photon emission computed tomography, DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition

polymerization-promoting protein impairment, inflammatory mechanisms, mitochondrial dysfunction, and *COQ2* mutations (2-6), the disease mechanism remains unclear, and there is no effective treatment for MSA. The second consensus statement on the diagnosis of multiple system atrophy in 2008 (Table 1) was widely accepted as a guideline for the diagnosis of MSA (7), and the criteria are referred to in the Practice Guidelines for Spinocerebellar Degeneration and Multiple System Atrophy 2018 in Japan (8). However, the criteria are considered insufficient in terms of sensitivity and specificity, particularly for early-stage disease. In a clinicopathological study examining the validity of the second consensus statement, the sensitivity and positive predictive value (PPV) for possible and probable MSA were 41%, 18%, 95%, and 100%, respectively, at the first evaluation and 92%, 63%, 89%, and 91% at the final evaluation. In two recent brain bank studies that assigned a diagnosis of possible or probable MSA according to the second consensus statement, the PPV at the final diagnosis was reported to be only 62% and 78.8%, respectively (9, 10). The most common misdiagnoses include Parkinson's disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy

(PSP), and corticobasal degeneration (9). However, the criteria have several other problems: they do not reflect the clinical heterogeneity of MSA and the exclusion criteria are unclear. In addition, new diagnostic markers were excluded from the criteria. In 2022, Wenning et al. proposed new diagnostic criteria (Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy, MDS criteria) (Table 2) to solve these problems (11). These criteria include a category of clinically established MSA, which is expected to improve specificity (for example, >90%) at the expense of sensitivity, and clinically probable MSA, which balances sensitivity (including the majority of MSA cases, > 80%) and specificity (excluding the majority of non-MSA cases, >80%). Importantly, a category of possible prodromal MSA has been suggested as a useful category for enrollment in clinical trials, that does not meet the two above-mentioned diagnostic criteria.

We established a regional MSA registry (Hokkaido Rare disease Consortium for MSA; HoRC-MSA) for clinical trials using data registered with the Japan Intractable Disease System. Several background points are relevant: (1) Hokkaido is a single autonomous island in Japan with low population movement; (2) the number of patients with MSA in Hokkaido was sufficient to conduct an epidemiological study (n=647, according to national data collected in 2014); and (3) many neurologists in Hokkaido have ensured a high intrinsic rate of cooperation from the prefecture (6). In total, 244 patients with MSA from 66 hospitals in Hokkaido were included in this study. The evaluation period was approximately ten years. The number of cases and observation period were comparable to those reported in other studies.

This study aimed to clarify the natural history of MSA and to provide basic data for clinical trials. Furthermore, we utilized patient data from HoRC-MSA to investigate trends in the number of patients in each category and the characteristics of the clinical features of the MDS criteria for MSA in comparison to the criteria in the second consensus statement.

## Materials and Methods

Between November 2014 and July 2022, patients diagnosed with MSA were recruited from 66 hospitals, including Hokkaido University Hospital in Hokkaido, Japan. The diagnoses of MSA were made by neurologists, and patients who consented to participation were enrolled in the HoRC-MSA study. Among the enrolled patients, those with additional clinical information, such as magnetic resonance imaging findings and symptom history, were selected. The two diagnostic criteria, namely the second consensus statement and MDS criteria, were retrospectively applied to these groups at three separate times: the first evaluation, the time of enrollment (diagnosis), and the most recent evaluation (final evaluation). The diagnosis of MSA was confirmed by neurologists based on the second consensus statement or the individual questionnaire for the designated intractable disease of MSA in Japan. Based on the diagnostic criteria, each patient was classified as having probable or possible MSA according to the second consensus criteria, and as having clinically established MSA, clinically probable MSA, or possible prodromal MSA according to the MDS criteria. At the diagnosis of MSA, patients were classified into two subtypes: MSA-C, with a predominance of cerebellar symptoms, and MSA-P, with a predominance of parkinsonism. Patients with neither of these subtypes were considered unclassifiable. Clinical assessments and investigations were performed by neurologists when patients with MSA were enrolled in the HoRC-MSA study or when neurodegenerative disease was strongly suspected. Periodic evaluations were performed for patients who could be followed-up continuously. The evaluation included autonomic disturbances (urinary incontinence, voiding difficulties, constipation, and orthostatic hypotension), neurological symptoms (parkinsonism and cerebellar ataxia), and scores on the Unified Multiple System Atrophy Rating Scale (UMSARS), Scale for the Assessment and Rating of Ataxia, Berg Balance Scale, MSA Health-Related Quality of Life Scale, and Scales for Outcomes in Parkinson's Disease-Autonomic. Laboratory tests included hematology, routine biochemistry, and other screening tests. The imaging studies included brain MRI, dopamine transporter scintigraphy, and N-isopropyl-p-($^{123}$I) iodoamphetamine single-photon emission computed tomography. However, the results of laboratory tests and imaging studies other than MRI performed at the time of enrollment in HoRC-MSA were not used in this study. Genetic screening to differentiate hereditary spinocerebellar degeneration was not performed for any of the patients.

This study was approved by the Institutional Review Board of Hokkaido University Hospital (approval number: 013-0208). Written informed consent was obtained from all the participants. Patients with severe cognitive impairment were excluded from this study.

The primary outcome was the evaluation of patient trends in each category of the MDS criteria in comparison to those of the second consensus statement at the first evaluation, the diagnosis, and the final evaluation. We also investigated the association between patient characteristics, clinical features, and each category of the new diagnostic criteria. In particular, we classified and examined categories that met (clinically established/clinically probable) or did not meet the diagnostic criteria (including possible prodromal) or phenotypes (MSA-C/MSA-P). In another analysis, we examined the correlations between the UMSARS Part II scores and the MDS criteria. The chi-square test and Pearson's chi-square test with Yates correction were used to assess differences between the criteria. Statistical significance was defined as $p< 0.05$, and the results were expressed as mean±standard deviation or median (interquartile range, IQR). IBM SPSS Statistics version 25.0 (IBM SPSS Statistics, Chicago, USA) and Statcel 2 (Microsoft, Redmond, USA) were used for to perform the analyses.

**Table 2. MDS Criteria (11).**

| | | |
|---|---|---|
| Essential features | A sporadic, progressive adult (>30years) onset disease. | |
| | **Clinically established MSA** | **Clinically probable MSA** |
| Core clinical features | 1. Autonomic dysfunction defined as (at least one is required)<br>・Unexplained voiding difficulties with post-void urinary residual volume ≥100mL<br>・Unexplained urinary urge incontinence<br>・Neurogenic OH (≥20/10 mmHg blood pressure drop) within 3 minutes of standing or head-up tilt test<br>and at least one of<br>1. Poorly L-dopa-responsive parkinsonism<br>2. Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, oculomotor features) | At least two of:<br>1. Autonomic dysfunction defined as (at least one is required):<br>・Unexplained voiding difficulties with post-void urinary residual volume<br>・Unexplained urinary urge incontinence<br>・Neurogenic OH (≥20/10 mmHg blood pressure drop) within 10 minutes of standing or head-uptilt test<br>2. Parkinsonism<br>3. Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features) |
| Supportive clinical (motor or non-motor) features | At least two | At least one |
| MRI marker | At least one | Not required |
| Exclusion criteria | Absence | Absence |
| Supportive features | Supportive motor features<br>・Rapid progression within 3 years of motor onset<br>・Moderate to severe postural instability within 3 years of motor onset<br>・Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia<br>・Severe speech impairment within 3 years of motor onset<br>・Severe dysphagia within 3 years of motor onset<br>・Unexplained Babinski sign<br>・Jerky myoclonic postural or kinetic tremor<br>・Postural deformities | Supportive non-motor features<br>・Stridor<br>・Inspiratory sighs<br>・Cold discolored hands<br>・Erectile dysfunction (below age of 60 years for clinically probable MSA)<br>・Pathologic laughter or crying |
| MRI markers of clinically established MSA | Each affected brain region as evidenced by either atrophy or increased diffusivity counts as one MRI marker | |
| | For MSA-P<br>• Atrophy of:<br>・Putamen (and signal decrease on iron-sensitive sequences)<br>・Middle cerebellar peduncle<br>・Pons<br>・Cerebellum<br>• “Hot cross bun” sign<br>• Increased diffusivity of:<br>・Putamen<br>・Middle cerebellar peduncle | For MSA-C<br>• Atrophy of:<br>・Putamen (and signal decrease on iron-sensitive sequences)<br>・Infratentorial structures (pons and middle cerebellar peduncle)<br>• “Hot cross bun” sign<br>• Increased diffusivity of:<br>・Putamen |
| Exclusion criteria | ・Substantial and persistent beneficial response to dopaminergic medications<br>・Unexplained anosmia on olfactory testing<br>・Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities<br>・Recurrent visual hallucinations not induced by drugs within 3 years of disease onset<br>・Dementia according to DSM-V within 3 years of disease onset<br>・Downgaze supranuclear palsy or slowing of vertical saccades<br>・Brain MRI findings suggestive of an alternative diagnosis (e.g., PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)<br>・Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient’s symptoms | |
| | **Possible prodromal MSA** | |
| Clinical non-motor features (entry criteria) | At least one of the following:<br>・RBD (polysomnography proven)<br>・Neurogenic OH (≥20/10 mmHg blood pressure drop) within 10 minutes of standing or head-up tilt<br>・Urogenital failure (erectile dysfunction in males below age of 60 years combined with at least one of unexplained voiding difficulties with post-void urinary residual volume>100 mL and unexplained urinary urge incontinence) | |
| Clinical motor features | At least one of the following:<br>・Subtle parkinsonian signs<br>・Subtle cerebellar signs | |
| Exclusion criteria | ・At least one of unexplained anosmia on olfactory testing or abnormal cardiac sympathetic imaging ($^{123}$I-MIBG scintigraphy)<br>・Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities<br>・Recurrent visual hallucinations not induced by drugs within 3 years of disease onset<br>・Dementia according to DSM-V within 3 years of disease onset<br>・Downgaze supranuclear gaze palsy or slowing of vertical saccades<br>・Brain MRI findings suggestive of an alternative diagnosis (e.g., PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)<br>・Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient’s symptoms | |

MDS criteria: Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy, MSA: multiple system atrophy, OH: orthostatic hypotension, MSA-C: MSA cerebellar dominant type, MSA-P: MSA parkinsonian dominant type, MRI: magnetic resonance imaging, DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition, PSP: progressive supranuclear palsy, RBD: rapid eye movement sleep behavior disorder, $^{123}$I-MIBG: $^{123}$I-metaiodonebzylguanidine

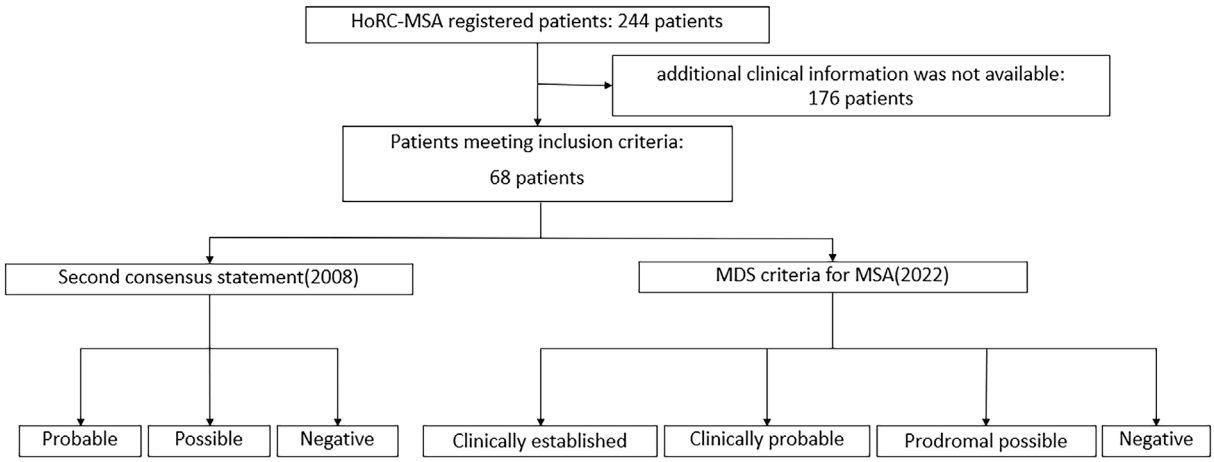


**Figure 1.** **Study flowchart. MSA: multiple system atrophy, HoRC-MSA: Hokkaido Rare Disease Consortium for MSA, MDS criteria: Movement Disorder Society Criteria for the Diagnosis of MSA**

**Table 3.** **Patient Characteristics.**

| Characteristic | First evaluation | Diagnosis | Final evaluation |
|---|---|---|---|
| **Age (years)** | 62.4±9.05 | 64.2±8.80 | 66.0±8.64 |
| **Sex (M:F)** | | 32:36 (47.1%:52.9%) | |
| **Disease duration (years)** | 2.46±2.35 | 3.75±2.98 | 6.02±3.79 |
| **MSA-C:MSA-P:Unclassifiable** | | 46:19:3 (67.6%:27.9%:4.4%) | |
| **UMSARS Part II** | | | |
| All patients | | 20.9±10.5 | |
| Clinically established | | 23.7±10.67 | |
| Clinically probable | | 20.8±8.82 | |
| Possible prodromal | | 10.5±7.42 | |
| Negative | | 12.0±3.96 | |

MSA: multiple system atrophy, M: male, F: female, MSA-C: MSA cerebellar dominant type, MSA-P: MSA parkinsonian dominant type, UMSARS: Unified Multiple System Atrophy Rating Scale

## Results

Of the 244 patients enrolled in the HoRC-MSA study, 227 were evaluated according to the diagnostic criteria of the second consensus statement, and 68 [male, n=32 (47.1%), female, n=36 (52.9%)], were eligible according to the MDS criteria (Fig. 1). The mean age was 62.4±9.0 years at the first evaluation, 64.2±8.8 years at the diagnosis, and 66.0±8.6 years at the final evaluation. The mean duration of disease (from disease onset) was 2.46±2.35 years at the first evaluation, 3.75±2.98 years at the diagnosis, and 6.02±3.79 years at the final evaluation. Furthermore, 46 patients (67.6%) were diagnosed with MSA-C, 19 (27.9%) with MSA-P, and three (4.4%) had features of both MSA-C and MSA-P at the initial evaluation (unclassifiable). The mean score of UMSARS part II at the diagnosis was 20.9±10.5 (Table 3).

### *1. The initial evaluation* (Fig. 2A, B)

The classifications of the 68 patients were as follows: clinically established MSA (n=27; 39.7%); clinically probable MSA (n=13; 19.1%); possible prodromal MSA (n=12; 17.6%); and negative [did not meet the criteria (n=16; 23.5%)]. Conversely, the classifications according to the second consensus statement were as follows: probable MSA (n =41; 60.2%); possible MSA (n=16; 23.5%); and negative (n =11; 16.2%). Approximately 20% of the patients did not have autonomic dysfunction at the initial evaluation and did not meet the diagnostic criteria. Some cases were classified as possible prodromal or negative because they did not meet the MDS criteria for supportive findings and were not clinically established or probable.

Of the patients classified as clinically established, 24 (88.9%) had probable MSA, and 3 (11.1%) were negative. Of the patients classified as clinically probable, 8 (61.5%) had probable MSA, 4 (30.8%) had possible MSA, and 1 (7.7%) was negative. Of the patients classified as possible prodromal, 9 (75.0%) hade probable MSA, and 3 (25.0%) had possible MSA. Among the patients who did not meet the MDS criteria, 6 (37.5%) were classified as possible MSA and 10 (62.5%) were classified as negative according to the new criteria. In the second consensus statement, some cases of possible MSA and negative cases were reclassified

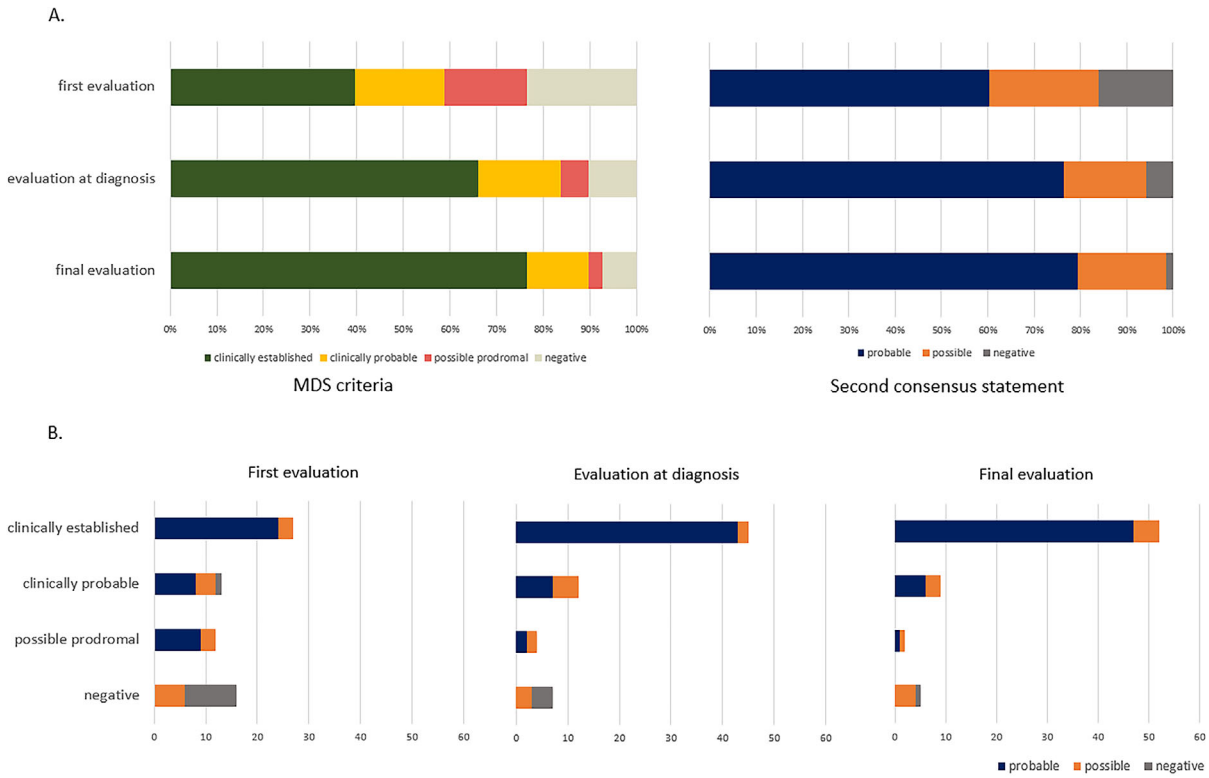


**Figure 2.** **(A) The percentage of patients diagnosed with MSA classified as clinically established, clinically probable, possible prodromal, and negative based on the MDS criteria for each category in the second consensus statement. (B) The number of patients classified into each diagnostic category of the two criteria. MDS criteria: The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy**

into the category with higher sensitivity and specificity in the MDS criteria, while some cases of probable MSA were classified into the category with lower specificity, such as possible prodromal cases. This trend was also observed at the diagnosis and at the final evaluation. However, at the time of the first evaluation, the categories of each diagnostic criterion were strongly correlated ($p<0.001$).

### *2. At the diagnosis and final evaluation* (Fig. 2A, B)

At the time of the diagnosis, the classifications, according to the MDS criteria, were as follows: clinically established (n=45; 66.2%); clinically probable (n=12; 17.6%); possible prodromal (n=4; 5.9%); and negative (n=7; 10.3%). According to the second consensus statement, the classifications were as follows: probable (n=52; 76.5%); possible (n=12; 17.6%); and negative (n=5; 7.4%). The number of patients who presented with symptoms corresponding to supportive findings such as autonomic dysfunction and rapid progression, increased and met the criteria for categories with high sensitivity and specificity. At the final evaluation, the classifications according to the MDS criteria were as follows: clinically established (n=52; 76.5%); clinically probable (n=9; 13.2%); possible prodromal (n=2; 2.9%); and negative (n=5; 7.4%). The classifications according to the second consensus statement were as follows: probable (n=54; 79.4%); possible (n=13; 19.1%); and negative (n=1; 1.6%). For both diagnostic criteria, the patient was consistently negative when the autonomic dysfunction was unremarkable. There was also a strong correlation between the MDS criteria and second consensus criteria category at the diagnosis and final evaluation ($p<0.001$).

### *3. The association between the clinical features used in the MDS criteria and each category or the MSA phenotypes.*

To determine the clinical profile of patients in each category of the MDS criteria, we evaluated the association and the significance of differences between each category and patient background factor (Table 4). Regarding patient characteristics, there were significant differences in age at the initial evaluation and disease duration, with patients with older age and longer disease duration tending to meet the diagnostic criteria. Among the phenotypes, MSA-P tended to meet the diagnostic criteria more frequently than MSA-C; however, the difference was not statistically significant. Table 5 shows the association and probability values for the clinical features used in the MDS criteria, and each category and phenotype at the initial evaluation. In patients classified as clinically established and clinically probable, autonomic features, including unexplained urinary urge incontinence, postvoid urinary residual of any volume, neurogenic orthostatic hypotension, poor levodopa responsiveness, atrophy of the

**Table 4. Features of Clinically Established/clinically Probable MSA and Possible Prodromal MSA/negative at First Evaluation.**

| | Clinically established and clinically probable MSA | Possible prodromal MSA and negative | p value |
|---|---|---|---|
| **Age (years)** | 64.23±8.04 | 59.79±9.59 | 0.046 |
| **Sex (n, %)** | | | |
| **Male** | 19 (59.4%) | 13 (40.6%) | 0.949 |
| **Female** | 21 (58.3%) | 15 (41.7%) | 0.952 |
| **Duration(years)** | 2.97±2.68 | 1.74±1.45 | 0.033 |
| **Phenotype (n, %)** | | | |
| **MSA-C** | 23 (50.0%) | 23 (50.0%) | 0.244 |
| **MSA-P** | 15 (78.9%) | 4 (21.1%) | 0.070 |

MSA: multiple system atrophy, MSA-C: MSA cerebellar dominant type, MSA-P: MSA parkinsonian dominant type

putamen, increased diffusivity of the middle cerebellar peduncle as an MRI marker, rapid progression, moderate to severe postural instability, severe speech impairment or dysphagia within 3 years of motor onset, unexplained Babinski sign, postural deformities, and erectile dysfunction, were more common. No significant differences were observed in any of the clinical features at the time of the diagnosis or at the final evaluation.

In the assessment of phenotypes at the first evaluation, there were no associations with autonomic features, whereas core parkinsonism features, atrophy of the putamen, increased diffusivity of the putamen as MRI markers, moderate-to-severe postural instability or severe dysphagia within 3 years of motor onset, craniocervical dystonia induced or exacerbated by L-dopa, jerky myoclonic postural or kinetic tremor, and postural deformities were significantly associated with MSA-P. No significant association was found between the clinical features and MSA-C.

### 4. Correlation between MDS criteria and UMSARS part II

The MDS criteria and UMSARS part II scores were significantly correlated (p=0.009); patients with higher scores tended to be classified as clinically established or clinically probable (Fig. 3).

## Discussion

In the current study, we assessed the 2022 MDS criteria in 68 patients with MSA and compared them to the criteria of the 2008 consensus statement. Our results confirm the utility of the MDS criteria. The MDS criteria were more stringent than the second consensus statement in terms of the numerical criteria for clinical features, making it more difficult for patients to be classified into highly specific categories, particularly at the initial evaluation. On the other hand, a new category, possible prodromal, has been added to cover suspected cases that do not qualify as clinically established or clinically probable. The possible prodromal patients were often reclassified as clinically established or clinically probable as their symptoms progressed, and continued follow-up was considered necessary.

Before the MDS criteria were published, the second consensus statement was criticized for several reasons (12). The first is related to diagnostic accuracy. In the second consensus statement, neuropathological evaluation was required for a definitive diagnosis, and an autopsy was necessary for the diagnosis of definite MSA. This problem can be solved by adding clinical features that improve the specificity. Diagnostic specificity can be ensured by identifying strongly supportive biomarkers, such as MRI and radioisotope findings, as well as autonomic failures, such as voiding difficulties and orthostatic hypotension, which are useful for making an early diagnosis. Other problems include the distinction between non-supportive and exclusion factors for MSA, the definition of L-dopa responsiveness, and the delineation of patients with less important features, such as family history and disease duration, as well as those with atypical variants or unremarkable autonomic failures.

The difference between the MDS criteria and the criteria of the second consensus statement may be attributed to the addition of MRI markers and the clarification of the exclusion criteria. The criterion for orthostatic hypotension improved in terms of both value and observation time, which increased its sensitivity. Furthermore, some patients with possible MSA based on the second consensus statement were newly classified as clinically established MSA based on the MDS criteria, which showed higher specificity. In contrast, some non-supportive features, such as onset after the age of 75 years and dementia, were eliminated, and some patients who did not meet the second consensus statement were classified according to the MDS criteria. Considering the high sensitivity and low specificity of possible prodromal MSA in the MDS criteria, active enrollment for clinical trials is possible at the initial evaluation by applying the classification of possible prodromal. If the diagnosis is not established at the first evaluation, repeated evaluations will lead to a definite diagnosis. This finding suggests that the issues mentioned in the second consensus statement have been addressed.

**Table 5. Statistical Correlations between the Clinical Features of the MDS Criteria and Each Category or MSA Phenotype at First Evaluation (n, %).**

| | Clinically established | Clinically probable | Possible prodromal | Negative | p value (CE, CP vs PP, ng) | MSA-C | MSA-P | p value |
|---|---|---|---|---|---|---|---|---|
| **Core autonomic features** | | | | | | | | |
| Unexplained urinary urge incontinence | 15 (56%) | 5 (38%) | 4 (33%) | 0 (0%) | **<0.001** | 17 (37%) | 6 (32%) | 0.740 |
| Unexplained voiding difficulties with post-void urinary residual volume >100 mL | 5 (19%) | 2 (15%) | 2 (17%) | 0 (0%) | 0.248 | 6 (13%) | 2 (11%) | 0.744 |
| Post-void urinary residual of any volume | 14 (52%) | 7 (54%) | 3 (25%) | 1 (6%) | **0.011** | 16 (35%) | 8 (42%) | 0.658 |
| Neurogenic OH | 21 (78%) | 6 (46%) | 9 (75%) | 0 (0%) | **0.049** | 24 (52%) | 10 (53%) | 0.941 |
| **Core cerebellar features** | | | | | | | | |
| Cerebellar dysarthria | 18 (67%) | 10 (77%) | 7 (58%) | 6 (38%) | 0.218 | 31 (67%) | 9 (47%) | 0.340 |
| Limb ataxia | 24 (89%) | 10 (77%) | 11 (92%) | 10 (63%) | 0.652 | 43 (93%) | 10 (53%) | 0.096 |
| Oculomotor dysfunction | 16 (59%) | 6 (46%) | 5 (42%) | 4 (25%) | 0.169 | 24 (52%) | 7 (37%) | 0.384 |
| Gait ataxia | 20 (74%) | 9 (69%) | 10 (83%) | 11 (69%) | 0.906 | 40 (87%) | 8 (42%) | 0.055 |
| **Core parkinsonian features** | | | | | | | | |
| Parkinsonism | 1 (4%) | 1 (8%) | 0 (0%) | 0 (0%) | 0.237 | 0 (0%) | 2 (11%) | **0.024** |
| Poor levodopa responsiveness | 14 (52%) | 2 (15%) | 0 (0%) | 4 (25%) | 0.054 | 2 (4%) | 17 (89%) | **<0.001** |
| **MRI markers** | | | | | | | | |
| Atrophy of putamen | 12 (44%) | 3 (23%) | 1 (8%) | 1 (6%) | **0.014** | 5 (11%) | 12 (63%) | **<0.001** |
| Atrophy of pons | 22 (81%) | 10 (77%) | 8 (67%) | 8 (50%) | 0.270 | 36 (78%) | 12 (63%) | 0.466 |
| Atrophy of middle cerebellar peduncle | 21 (78%) | 12 (92%) | 8 (67%) | 10 (63%) | 0.393 | 38 (83%) | 11 (58%) | 0.295 |
| Atrophy of cerebellum | 25 (93%) | 12 (92%) | 10 (83%) | 11 (69%) | 0.442 | 43 (93%) | 13 (68%) | 0.318 |
| "Hot cross bun" sign | 22 (81%) | 8 (62%) | 9 (75%) | 7 (44%) | 0.378 | 37 (80%) | 7 (37%) | 0.052 |
| Increased diffusivity of putamen | 11 (41%) | 3 (23%) | 1 (8%) | 4 (25%) | 0.188 | 3 (7%) | 16 (84%) | **<0.001** |
| Increased diffusivity middle cerebellar peduncle | 19 (70%) | 10 (77%) | 4 (33%) | 6 (38%) | **0.049** | 30 (65%) | 9 (47%) | 0.363 |
| **Supportive motor features** | | | | | | | | |
| Rapid progression within 3 years of motor onset | 15 (56%) | 3 (23%) | 0 (0%) | 0 (0%) | **<0.001** | 10 (22%) | 8 (42%) | 0.143 |
| Moderate to severe postural instability within 3 years of motor onset | 18 (67%) | 6 (46%) | 0 (0%) | 1 (6%) | **<0.001** | 13 (28%) | 12 (63%) | **0.034** |
| Severe speech impairment within 3 years of motor onset | 6 (22%) | 1 (8%) | 0 (0%) | 0 (0%) | **0.027** | 6 (13%) | 1 (5%) | 0.370 |
| Severe dysphagia within 3 years of motor onset | 6 (22%) | 2 (15%) | 0 (0%) | 0 (0%) | **0.018** | 3 (7%) | 5 (26%) | **0.034** |
| Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia | 2 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.237 | 0 (0%) | 2 (11%) | **0.024** |
| Unexplained Babinski sign | 18 (67%) | 5 (38%) | 0 (0%) | 3 (19%) | **0.002** | 16 (35%) | 10 (53%) | 0.276 |
| Jerky myoclonic postural or kinetic tremor | 2 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.237 | 0 (0%) | 2 (11%) | **0.024** |
| Postural deformities | 8 (30%) | 2 (15%) | 0 (0%) | 1 (0%) | **0.031** | 1 (2%) | 10 (53%) | **<0.001** |
| **Supportive non-motor features** | | | | | | | | |
| Stridor | 7 (26%) | 0 (0%) | 0 (0%) | 1 (6%) | 0.099 | 4 (9%) | 3 (16%) | 0.427 |
| Inspiratory sighs | 3 (11%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.149 | 1 (2%) | 2 (11%) | 0.144 |
| Cold discolored hands and feet | 1 (4%) | 1 (8%) | 0 (0%) | 0 (0%) | 0.237 | 2 (4%) | 0 (0%) | 0.351 |
| Erectile dysfunction | 10 (37%) | 3 (23%) | 0 (0%) | 0 (0%) | **0.003** | 9 (20%) | 2 (11%) | 0.390 |
| Pathologic laughter or crying | 1 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.403 | 0 (0%) | 1 (5%) | 0.111 |

MSA: multiple system atrophy, CE: clinically established MSA, CP: clinically probable MSA, PP: possible prodromal MSA, ng: negative, MSA-C: MSA cerebellar dominant type, MSA-P: MSA parkinsonian dominant type, OH: orthostatic hypotension, MRI: magnetic resonance imaging

With regard to the individual categories of the MDS criteria and patient characteristics at the first evaluation, there were significant differences in age and disease duration in the patient characteristics, suggesting that the diagnosis becomes easier at an advanced stage. Regarding the association between clinical features and each category, each clinical feature had a strong relationship with clinically established MSA and clinically probable MSA in patients diagnosed with the condition, especially in those with autonomic dysfunction and supportive findings, which are highly specific and useful for making an early diagnosis. In the assessment of the MSA phenotype, more clinical features were significantly associated with MSA-P than with MSA-C. This suggests that cerebellar symptoms appear relatively early in patients with MSA-P, whereas parkinsonism is less prominent in patients with MSA-C, even in the advanced stages of

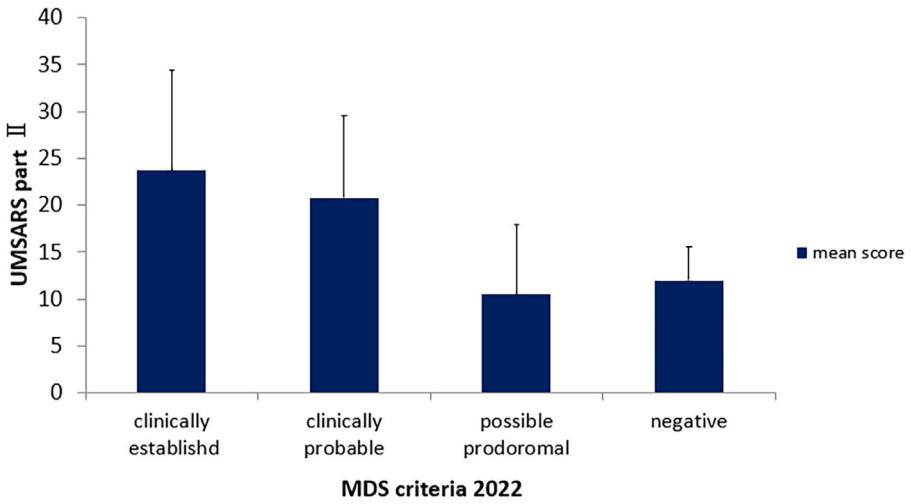


**Figure 3. Correlation between the MDS criteria and UMSARS part II scores. Patients with higher scores were classified as clinically established or clinically probable. MDS criteria: The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy, UMSARS: Unified Multiple System Atrophy Rating Scale**

the disease.

The main limitations of the present study are as follows. First, the MDS criteria included additional evaluation features and laboratory tests. Because this study was retrospective in nature, we could not assess some of the features, especially the supportive clinical features and biomarkers. Therefore, information could not be obtained from the medical records or examined. In particular, the tilt test, residual urine measurement, and presence of rapid eye movement sleep behavior disorder by polysomnography were not always evaluated at the initial evaluation, and there may have been false-negative results for autonomic dysfunction and non-motor findings. Second, since the tilt test assessment was performed within 2-3 minutes (and not within 10 minutes) for orthostatic hypotension, some patients with unclassifiable and possible prodromal MSA may be included in the clinically probable MSA or highly specific classification. Third, the MDS criteria and second consensus statements were evaluated from the viewpoint of the clinical course, and no autopsies or brain biopsies were performed. Therefore, the definitive diagnosis in this study could have been different because a pathological examination was not performed. In particular, the second consensus statement and the individual questionnaire for intractable diseases were utilized for enrollment in this study. This fact makes the interpretation somewhat broad, since constipation, which is not included in both diagnostic criteria, may be used as a clinical feature of autonomic dysfunction. However, Virameteekul et al. (13) and Sekiya et al. (14) performed a pathological evaluation of the usefulness of MDS criteria. In these studies, the sensitivity of the clinically established and clinically probable classifications was 20.4% and 62.1% (13), respectively, and 16% and 64% (14). The specificity of the clinically established and clinically probable classifications was 100% and 95.3% (13), respectively, and 99% and 74% (14). Therefore, the patients enrolled in this study generally met the diagnostic criteria from the early stages of disease onset, and a high rate of positive diagnoses was expected. This clinical study allowed us to follow the transitions between the categories of each diagnostic criterion over time, and we believe that this evaluation is more practical.

## Conclusion

As the 2022 MDS criteria included MRI and supportive findings and described the exclusion criteria, the MDS criteria were more specific than the second consensus statement. In addition to being clinically established and clinically probable because they are considered to have high sensitivity and specificity, the new category of possible prodromal has made it easier to prevent underdiagnoses and is a highly useful diagnostic criterion for selecting patients for future clinical trials of disease-modifying therapies.

**The authors state that they have no Conflict of Interest (COI).**

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