RESEARCH ARTICLE

Impact of Magnetic Resonance Imaging Markers on the Diagnostic Performance of the International Parkinson and Movement Disorder Society Multiple System Atrophy Criteria

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ABSTRACT: Background: Multiple system atrophy is a neurodegenerative disease with α-synuclein aggregation in glial cytoplasmic inclusions, leading to dysautonomia, parkinsonism, and cerebellar ataxia.

Objective: The aim of this study was to validate the accuracy of the International Parkinson and Movement Disorder Society Multiple System Atrophy clinical diagnostic criteria, particularly considering the impact of the newly introduced brain magnetic resonance imaging (MRI) markers.

Methods: Diagnostic accuracy of the clinical diagnostic criteria for multiple system atrophy was estimated retrospectively in autopsy-confirmed patients with multiple system atrophy, Parkinson's disease, progressive supranuclear palsy, and corticobasal degeneration.

Results: We identified a total of 240 patients. Sensitivity of the clinically probable criteria was moderate at symptom onset but improved with disease duration (year 1: 9%, year 3: 39%, final ante mortem record: 77%), whereas their specificity remained consistently high (99%–100% throughout). Sensitivity of the clinically established criteria was low during the first 3 years (1%–9%), with mild improvement at the final ante mortem record (22%), whereas specificity remained high (99%–100% throughout). When MRI features were excluded from the clinically established criteria, their sensitivity increased considerably (year 1: 3%, year 3: 22%, final ante mortem record: 48%), and their specificity was not compromised (99%–100% throughout).

Conclusions: The International Parkinson and Movement Disorder Society multiple system atrophy diagnostic criteria showed consistently high specificity and low to moderate sensitivity throughout the disease course. The MRI markers for the clinically established criteria reduced their sensitivity without improving specificity. Combining clinically probable and clinically established criteria, but disregarding MRI features, yielded the best sensitivity with excellent specificity and may be most appropriate to select patients for therapeutic trials.

Key Words: multiple system atrophy; autopsy-confirmed; brain magnetic resonance imaging; MRI

Introduction

Multiple system atrophy (MSA) is a rare neurodegenerative disease with an estimated prevalence between 3.4 and 4.9 per 100,000 individuals, increasing to 7.8 per 100,000 among persons older than 40 years.[1,2] The mean survival time from symptom onset to death is 6 to 10 years.[3,4] There are limited symptomatic therapies available and no disease-modifying therapy to stop or slow disease progression.[1,5,6]

MSA presents with a variable combination of dysautonomia, parkinsonism, and cerebellar ataxia.[1] Based on the predominant symptoms, MSA can be classified into MSA with predominant parkinsonism or MSA with predominant cerebellar features.[7] Symptoms are caused by the progressive degeneration of neurons in several parts of the brain, including the substantia nigra, striatum, inferior olivary nucleus, pons, and cerebellum.[7-10] The lesions are not limited to these most consistently and severely affected brain areas, but may involve many other parts of the central, peripheral, and autonomic nervous systems, emphasizing the multisystem character of MSA. The histological hallmarks are glial cytoplasmic inclusions in oligodendroglia and neuronal cytoplasmic aggregates containing misfolded protein α-Synuclein.[11]

The second consensus criteria for the diagnosis of MSA by Gilman et al[7] in 2008 were widely recognized as the reference standard for clinical routine and research, but they were compromised by low to moderate sensitivity at early disease stages and moderate diagnostic accuracy in studies with autopsy-confirmed MSA patients.[12-14] In an attempt to improve the early and accurate clinical disease detection, novel International Parkinson and Movement Disorder Society (MDS) criteria for the clinical diagnosis of MSA have been proposed by Wenning et al[15] in 2022. In these, the diagnostic categories clinically probable, clinically established, and possible prodromal were introduced.[15] The aim of the latter is to cover the earliest possible stages of the disease.[15]

Previously, magnetic resonance imaging (MRI) studies have shown characteristic changes in various parameters and brain regions in MSA.[16-20] These imaging studies have shown specific atrophy patterns in MSA, including pontine and putaminal atrophy, and in some cases atrophy of the cerebellum.[18,21] Therefore, brain MRI markers have now been added as part of the new MDS-MSA diagnostic criteria for the diagnostic category of clinically established MSA.[15]

The new MDS-MSA clinical diagnostic criteria have meanwhile been validated against the neuropathological diagnostic gold standard in two independent reports, but the value of the MRI markers for their diagnostic accuracy has not been addressed so far.[22,23]

We aimed to validate the accuracy of the 2022 MDS-MSA criteria in a retrospective clinicopathological multicenter study with a particular focus on the impact of the newly introduced imaging features.

Patients and Methods

Patients

Cases with a pathological diagnosis of MSA,[24] Lewy body disease with a clinical diagnosis of Parkinson's disease (PD),[25] progressive supranuclear palsy (PSP),[26-28] or corticobasal degeneration (CBD)[27,29] and detailed longitudinal information in their clinical charts were identified from collaborating brain banks (Ludwig-Maximilians-University, Munich, Germany; King's College, London, UK; Lund University, Lund, Sweden; Erasmus Medical Center, Rotterdam, the Netherlands; Hospital Clinic–August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; Johns Hopkins University, Baltimore, MD; University of Pennsylvania, Philadelphia, PA; University of Toronto, Toronto, Ontario, Canada; sample overview: Supporting Information Table S1). Ethical approval had been obtained from all responsible ethics committees. All donors and/or relatives provided written informed consent for the scientific use of their brains and medical records.

Clinical Data

Detailed clinical information was obtained for each case by retrospective chart review. Patients had been regularly assessed throughout their disease course, and clinical diagnosis ante mortem had been established by specialists in movement disorders in secondary/tertiary care settings. The focus of data extraction from the patients' medical records was on autonomic features, parkinsonian, and cerebellar symptoms, as specified in the 2022 MDS-MSA criteria and 2008 second consensus criteria. The clinical information was systematically extracted according to Supporting Information Table S2. Patients were diagnosed with MSA post mortem.[15] Clinical symptoms were documented for each year since disease onset, respectively.

MRI Analyses

The presence of MRI features supporting an MSA diagnosis is required to establish a diagnosis of clinically established MSA by the MDS-MSA criteria.[15] The MRI features include atrophy of cerebellum, atrophy of middle cerebellar peduncle, atrophy of pons, atrophy of putamen (and signal decrease on iron-sensitive sequences), hot cross bun sign, increased diffusivity of putamen, and increased diffusivity of middle cerebellar peduncle. Those features were abstracted from both radiology reports and interpretations by physicians in primary centers with experience in movement disorders. To analyze the relevance of pathological MRI data on the diagnostic performance of MDS-MSA criteria, we calculated sensitivity and specificity for clinically established MSA in all patients and also only in those patients where MRI data were available. In the latter group, we calculated sensitivity and specificity of clinically established MSA with and without consideration of MRI features (ie, we simulated core clinical features and supportive clinical features of MDS-MSA diagnostic criteria to be sufficient for clinically established MSA).

Clinicopathological Validation

All cases with neuropathological diagnoses of MSA, PD, PSP, and CBD were retrospectively assigned to the clinical diagnostic categories possible prodromal, clinically established MSA, clinically probable MSA, or no MSA according to the MDS-MSA criteria[15] and to the categories possible MSA, probable MSA, or no MSA according to the second consensus criteria.[7] We calculated sensitivity, specificity, positive predictive value, and negative predictive value for the clinical diagnostic categories[7] in year 1, 2, 3, 6, and 9 after symptom onset, as well as for the final ante mortem record. We refrained from analyzing the clinical diagnostic category possible prodromal because of the small number of cases in our series (n = 11).

Statistical Analysis

To compare nonparametric demographic data (age of onset, age of death, disease duration) between MSA, PD, PSP, and CBD, we performed Kruskal-Wallis test and appropriate post hoc test. Significance was set at $P < 0.05$. All statistical analyses were performed using SPSS software, versions 23.0 and 28.0.1.1 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of All Included Patients

We identified 180 patients with a neuropathological diagnosis of MSA (Supporting Information Fig. S1). Sufficient clinical details were available for 144 of them to be included in the current analyses.

Correct clinical ante mortem MSA diagnosis of pathologically confirmed MSA cases was made in 26% (n = 38) at disease onset and in 81% (n = 117) at final ante mortem examination by movement disorder experts.

MRI data were available for 60% (n = 87) of all patients with MSA, with 72% (n = 63) of them fulfilling morphological/imaging criteria for MSA.

The disease control group of patients with neuropathological diagnoses other than MSA consisted of PD (40%, n = 39), CBD (18%, n = 17), and PSP (42%, n = 40).

Pathologically confirmed patients with MSA had a significant earlier disease onset and age of death compared with pathologically confirmed patients with PSP. Age of death of patients with MSA was also significantly earlier compared with patients with PD. Pathologically confirmed patients with PD had a significantly longer disease duration compared with patients with MSA, CBD, and PSP.

The detailed demographic data of all 240 patients are presented in Table 1.

Diagnostic Performance of MDS-MSA Criteria for Clinically Probable MSA and Clinically Established MSA

Sensitivity, specificity, positive predictive value, and negative predictive value of the clinically probable and clinically established MDS-MSA criteria, as well as possible and probable second consensus criteria as function of disease duration from onset of the first symptom related to MSA, are listed in Table 2.

The clinically probable criteria had a sensitivity of 9% in year 1, increasing to 39% in year 3 and 77% at the final ante mortem record. The specificity of these criteria was high during the entire disease course (99%–100% throughout).

The clinically established criteria had lower sensitivity, especially during the first 3 years after symptom onset (1%–9%), with a mild increase to 22% at final ante mortem record. The specificity of these criteria was perfect during the entire disease course (100% throughout).

Impact of MRI Data on Diagnostic Performance of Clinically Established MSA

Next, we analyzed the impact of the MRI markers of MSA, which are a mandatory component of the clinically established MDS-MSA criteria.

TABLE 1 *Demographic data*

Characteristics	MSA	All Non-MSA	PD	CBD	PSP
n	144	96	39	17	40
M:F, n [%]	61:83 [42.4:57.6]	61:35 [63.5:36.5]	25:14 [64.1:35.9]	10:7 [58.8:41.2]	26:14 [65.0:35.0]
Age of onset, y, mean ± SEM [range; median]	57.42 ± 8.43 [35–80; 58]	62.06 ± 10.19 [33–93; 61]	60.03 ± 12.76 [33–93; 61]	60.35 ± 6.75 [48–71; 59]	64.75 ± 8.01★ [49–81; 62]
Age of death, y, mean ± SEM [range; median]	64.94 ± 7.66 [40–90; 65]	72.91 ± 8.18 [56–95; 74]	77.38 ± 7.14★ [62–95; 78]	65.88 ± 7.02 [56–77; 68]	71.78 ± 6.98★ [59–87; 71]
Disease duration, y, mean ± SEM [range; median]	7.51 ± 3.23 [2–20; 7]	10.84 ± 8.49 [0–43; 8]	17.36 ± 10.40★ [1–43; 17]	5.53 ± 3.59★ [0–15; 5]	7.03 ± 3.13 [1–14; 7]
MRI data available, n [%]	87 [60.4%]	67 [69.8%]	16 [41%]	16 [94.1%]	35 [87.5%]
MRI suggesting MSA according to MDS-MSA criteria, n [%]	63 [72%]	3 [4%]	1 [6%]	1 [6%]	1 [2.9%]

Note: Demographic data of all autopsy-confirmed patients, subgrouped according to underlying pathology. Data are mean ± SD [range].
Kruskal–Wallis test followed by post hoc LSD test: ★$P < 0.05$ versus MSA.
Abbreviations: MSA, multiple system atrophy; PD, Parkinson's syndrome; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; M, male; F, female; SEM, standard error of the mean; MRI, magnetic resonance imaging.

TABLE 2 *Diagnostic values for different categories of MDS-MSA and second consensus MSA criteria*

Year after Disease Onset and Diagnostic Criteria	1	2	3	6	9	Final Record
Sensitivity						
MDS, clinically probable MSA	0.09	0.23	0.39	0.63	0.73	0.77
MDS, clinically established MSA	0.01	0.02	0.09	0.17	0.20	0.22
MDS, clinically probable and clinically established MSA	0.09	0.23	0.39	0.63	0.73	0.77
Second consensus, possible MSA	0.09	0.2	0.34	0.57	0.67	0.70
Second consensus, probable MSA	0.07	0.2	0.31	0.54	0.61	0.63
Second consensus, possible and probable MSA	0.11	0.24	0.41	0.66	0.77	0.78
Specificity						
MDS, clinically probable MSA	1	0.99	0.99	0.99	0.99	0.99
MDS, clinically established MSA	1	1	1	1	1	1
MDS, clinically probable and established MSA	1	0.99	0.99	0.99	0.99	0.99
Second consensus, possible MSA	0.99	0.98	0.95	0.95	0.92	0.94
Second consensus, probable MSA	0.98	0.97	0.96	0.97	0.96	0.97
Second consensus, possible and probable MSA	0.98	0.97	0.95	0.95	0.92	0.94
PPV						
MDS, clinically probable MSA	1	0.97	0.98	0.99	0.99	0.99
MDS, clinically established MSA	1	1	1	1	1	1
MDS, clinically probable and established MSA	1	0.97	0.98	0.99	0.99	0.99
Second consensus, possible MSA	0.92	0.93	0.90	0,94	0.93	0.94
Second consensus, probable MSA	0.83	0.90	0.92	0.96	0.96	0.97
Second consensus, possible and probable MSA	0.88	0.92	0.92	0.95	0.94	0.95
NPV						
MDS, clinically probable MSA	0.43	0.47	0.53	0.65	0.72	0.75
MDS, clinically established MSA	0.41	0.41	0.43	0.45	0.46	0.47
MDS, clinically probable and established MSA	0.43	0.47	0.53	0.65	0.72	0.75
Second consensus, possible MSA	0.42	0.45	0.49	0.59	0.65	0.67
Second consensus, probable MSA	0.41	0.45	0.48	0.58	0.62	0.63
Second consensus, possible and probable MSA	0.42	0.46	0.52	0.65	0.73	0.73

Abbreviations: MDS, International Parkinson and Movement Disorder Society; MSA, multisystem atrophy; PPV, positive predictive value; NPV, negative predictive value.

This analysis included only patients for which a detailed report of the MRI features relevant to the MDS-MSA diagnostic criteria or findings suggesting alternative diagnoses was available from a specialized neuroradiologist.

The numbers of patients per group with MRI data available and the number of MRIs thereof suggesting MSA according to MDS-MSA criteria are shown in Table 1.

Positive MRI features according to 2022 MDS-MSA criteria of all MSA patients receiving either diagnosis of clinically established or clinically probable MSA are listed in Table 3. According to the 2022 MDS-MSA criteria, atrophy or increased diffusivity in at least one of the determined brain regions counted as a positive MRI feature. One positive MRI feature was sufficient for the diagnosis of a clinically established MSA. Cerebellar atrophy was reported most often in all subgroups. By definition, MRI findings suggesting MSA according to the MDS-MSA criteria were present in all patients diagnosed as clinically established MSA. The absence of findings suggesting MSA according to MDS-MSA criteria was described in 51% of autopsy-confirmed MSA patients diagnosed as clinically probable MSA.

TABLE 3 *Pathological MRI markers according to 2022 MDS-MSA, as documented in the neuroradiological reports of autopsy-confirmed MSA patients fulfilling the clinical probable and clinically established criteria*

	Clinically Probable MSA (n = 39)		Clinically Established MSA (n = 34)	
MRI Markers	**n**	**%**	**n**	**%**
Cerebellar atrophy	17	44	25	74
Middle cerebellar peduncle atrophy	9	23	17	50
Pontine atrophy	11	28	21	62
Putaminal atrophy	6	15	12	35
Hot cross bun sign	6	15	11	32
Increased diffusivity of middle cerebellar peduncle on MRI	3	8	5	15
Increased diffusivity of putamen on MRI	1	3	1	3
Presence of any finding suggesting MSA according to MDS-MSA criteria	19	49	25	100
Absence of all findings suggesting MSA according to MDS-MSA criteria	20	51	0	0

Abbreviations: MRI, magnetic resonance imaging; MDS, International Parkinson and Movement Disorder Society; MSA, multisystem atrophy; PPV, positive predictive value; NPV, negative predictive value.

To analyze the impact of these MRI data on the diagnostic performance of MDS-MSA criteria, we calculated sensitivity and specificity for clinically established MSA with and without consideration of these MRI features (Table 4).

Clinically established criteria without consideration of MRI features showed a higher sensitivity as compared with the criteria considering the MRI features (Table 4). Disregard of the MRI data had only minimal influence on the specificity of clinically established MSA criteria, which was excellent with or without MRI data (99%–100% throughout).

Discussion

In 2018, the MSA Criteria Revision Task Force was established by the International Parkinson and Movement Disorder Society to guide the development of the new criteria to improve diagnostic accuracy in clinical MSA patients.[15] The diagnostic MSA criteria revision process had been carried out with a focus on multidisciplinary input and evidence-based decision-making.[30-33] A literature review has been conducted to provide evidence for the criteria revision.[3] The new criteria define four levels of diagnostic certainty: neuropathologically established MSA, clinically established MSA, clinically probable MSA, and possible prodromal MSA. These levels aimed to balance specificity and sensitivity for MSA diagnosis. The criteria introduced a new research category of possible prodromal MSA and supportive brain MRI markers.[15] The main structural MRI changes frequently associated with MSA included the hot cross bun and putaminal rim signs, as well as putaminal, pontine, and middle cerebellar peduncle atrophy. The latter imaging signs have now found their way into the diagnostic criteria.

We validated these criteria in a retrospective clinicopathological multicenter study in n = 240 patients with autopsy-confirmed diagnosis. The diagnostic performance of the MDS-MSA criteria for clinically probable MSA and clinically established MSA was evaluated with special consideration of the newly introduced imaging parameters for diagnosis of clinically established MSA.

In line with two other MDS-MSA criteria validation reports,[22,23] we found an excellent specificity; however, we found only moderate sensitivity across the different disease stages. Clinically probable MSA had a low sensitivity of 9% in the first year and improved to moderate levels of 39% in year 3 and 77% at the final record, with high specificity (99%–100%) throughout the disease course. Clinically established MSA had low sensitivity, especially in the first 3 years (1%–9%), with slight improvement at later stages (22% at the final ante mortem record), whereas specificity remained consistently high (100%).

Also, the 2008 second consensus diagnostic criteria of MSA demonstrated excellent specificity but limited sensitivity throughout the entire clinical course.

The best sensitivity in combination with high specificity was obtained by accepting either the 2008 second consensus criteria category possible and probable (ie,

TABLE 4 *Impact of MRI data on diagnostic performance of the clinically established MSA category according to the 2022 MDS-MSA criteria*

Year after Disease Onset and Diagnostic Criteria	1	2	3	6	9	Final Record
Sensitivity						
All patients included						
MDS, clinically established MSA, MRI features considered	0.01	0.02	0.09	0.17	0.20	0.22
MDS, clinically established MSA, MRI features not considered	0.02	0.09	0.19	0.36	0.41	0.43
MDS, clinically probable MSA and clinically established MSA, MRI features not considered	0.09	0.23	0.39	0.63	0.73	0.77
Only patients with MRI available included						
MDS, clinically established MSA, MRI features considered	0.01	0.03	0.14	0.26	0.31	0.33
MDS, clinically established MSA, MRI features not considered	0.03	0.10	0.22	0.38	0.45	0.48
MDS, clinically probable MSA and clinically established MSA, MRI features not considered	0.10	0.26	0.45	0.67	0.76	0.80
Specificity						
All patients included						
MDS, clinically established MSA, MRI features considered	1	1	1	1	1	1
MDS, clinically established MSA, MRI features not considered	1	1	1	0.99	0.99	0.99
MDS, clinically probable MSA and clinically established MSA, MRI features not considered	1	0.99	0.99	0.99	0.99	0.99
Only patients with MRI available included						
MDS, clinically established MSA, MRI features considered	1	1	1	1	1	1
MDS, clinically established MSA, MRI features not considered	1	1	1	0.99	0.99	0.99
MDS, clinically probable MSA and clinically established MSA, MRI features considered	1	0.99	0.99	0.99	0.99	0.99

Abbreviations: MRI, magnetic resonance imaging; MSA, multiple system atrophy; MDS, International Parkinson and Movement Disorder Society.

either of them; Table 2) or the 2022 MDS criteria clinically probable and clinically established (either of them), disregarding the MRI features (Table 4). Either of these criteria appears equally suitable for selecting patients for therapeutic trials, for which high specificity is an essential prerequisite.

We tend to assume that with clinical criteria alone a further increase in sensitivity might be almost impossible to achieve without compromising specificity, because of the broad spectrum of clinical manifestations MSA may take. Development of future diagnostic criteria to achieve both high sensitivity and specificity in the early clinical or even preclinical course of MSA will very likely have to rely on a biomarker-based diagnosis, to be developed in the future.

The impact of MRI findings in autopsy-confirmed MSA cases had previously been assessed.[14,34,35] Overall, structural brain MRI abnormalities were moderately specific for the disease but suboptimal regarding sensitivity, particularly in early stages. The two studies validating the 2022 MDS-MSA criteria do not provide detailed information on the MRI findings per single category.[22,23]

Limitations of this study are those of all retrospective clinicopathological studies, ie, nonstandardized evaluation, documentation, and the missing blinding of the neuroradiologists who analyzed the MRIs. In addition, the neuroradiologists evaluated MRI scans of MSA patients who had not yet been diagnosed at that time, so there is a possibility that MRI scans at the later time points could have yielded different results.

Therefore, prospective studies are needed to entirely evaluate the new 2022 MDS-MSA criteria. A particular strength of this study is the collection of autopsy-confirmed cases and corresponding clinical records from different brain banks and clinical and neuroradiological departments with high expertise in neurodegenerative diseases. Indeed, the current clinicopathological validation of the 2022 MDS-MSA criteria is the first clinicopathological validation of the new criteria taking explicitly into account the mandatory MRI markers for clinically established MSA. Further improvements may be made if the particular engagement of white matter is assessed in radiological-pathological comparisons.

Conclusions

The contribution of imaging data to the diagnosis of clinically established MSA appears of limited value. The sensitivity of clinically established MSA increased when MRI data were excluded from the criteria, eg, at the final ante mortem record from of 33% to 48%. Moreover, specificity remained unaffected at a very high level when MRI markers were not considered (99%–100% throughout). In summary, omission of the MRI markers from the criteria for clinically established MSA increased their sensitivity but did not compromise their specificity, because the clinical criteria alone already provided excellent specificity by themselves. This information is of relevance for both clinical routine and clinical research. ■

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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