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REVIEW

Diagnosis and differential diagnosis of MSA: boundary issues

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Abstract Because the progression of multiple system atrophy (MSA) is usually rapid and there still is no effective cause-related therapy, early and accurate diagnosis is important for the proper management of patients as well as the development of neuroprotective agents. However, despite the progression in the field of MSA research in the past few years, the diagnosis of MSA in clinical practice still relies largely on clinical features and there are limitations in terms of sensitivity and specificity, especially in the early course of the disease. Furthermore, recent pathological, clinical, and neuroimaging studies have shown that (1) MSA can present with a wider range of clinical and pathological features than previously thought, including features considered atypical for MSA; thus, MSA can be misdiagnosed as other diseases, and conversely, disorders with other etiologies and pathologies can be clinically misdiagnosed as MSA; and (2) several investigations may help to improve the diagnosis of MSA in clinical practice. These aspects should be taken into consideration when revising the current diagnostic criteria. This is especially true given that disease-modifying treatments for MSA are under investigation.

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Introduction

Multiple system atrophy (MSA) is an adult-onset sporadic neurodegenerative disorder characterized by any combination of parkinsonism, cerebellar ataxia, and autonomic failure [1]. Because the progression of MSA is usually rapid and relentless with a mean survival of 6–10 years [2, 3] and there still is no effective disease-modifying therapy, early and accurate diagnosis is crucial not only for the optimal management of patients but also for the development of therapeutic strategies. Despite the progress in the field of MSA research in the past few years, the diagnosis of MSA in clinical practice still relies largely on clinical symptoms and signs. However, recent pathological and clinical studies have reported the following findings: (1) patients with MSA can present with a wider range of clinical features and have more variable disease courses than previously thought, including features considered atypical for MSA; (2) pathological changes vary more than previously described in terms of the regions involved as well as the degrees of neurodegeneration, and (3) neuroimaging and electrophysiological tests used for the diagnosis of MSA in clinical practice can be misleading [4–11]. Thus, disorders with other etiologies and pathologies can be clinically misdiagnosed as MSA, and conversely, MSA can be misdiagnosed as other diseases.

To this end, we review recent advances regarding the clinical, pathological, and neuroimaging features of MSA regarding the current diagnostic criteria [12] and discuss the problems and difficulties that hamper the diagnosis and differential diagnosis of MSA.

Current diagnostic criteria and their problems

Clinical diagnostic criteria

As in other neurodegenerative disorders, a definite diagnosis of MSA is based on a postmortem pathological confirmation. However, in clinical practice, a definite diagnosis cannot be reached for obvious reasons, and clinicians have to rely on the suggested clinical diagnostic criteria which include clinical features and, when needed, neuroimaging features [12]. Clinical features for a diagnosis of MSA consist of autonomic failure in combination with motor symptoms. Autonomic failure in MSA includes cardiovascular dysfunction, genitourinary dysfunction, thermoregulatory and sudomotor dysfunction, fecal incontinence and constipation, and sleep-disordered breathing [1, 13], among which orthostatic hypotension or urinary symptoms are required for the diagnosis. Motor symptoms include poorly levodopa-responsive parkinsonism or cerebellar ataxia. A diagnosis of probable MSA is made when a patient has urinary incontinence or an orthostatic decrease in blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic in addition to motor symptoms. If the autonomic dysfunction of the patient does not meet this requirement, a diagnosis of possible MSA is made, but only when there is at least one of the "additional" clinical or neuroimaging features (Table 1) because without it, the specificity of the diagnosis will decrease, and MSA will be overdiagnosed.

Table 1 Additional features of possible MSA [12]

Possible MSA-P or MSA-C
Babinski sign with hyperreflexia
Stridor
Possible MSA-P
Rapidly progressive parkinsonism
Poor response to levodopa
Postural instability within 3 years of motor onset
Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
Dysphagia within 5 years of motor onset
Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C
Parkinsonism (bradykinesia and rigidity)
Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
Hypometabolism on FDG-PET in putamen
Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

However, current clinical diagnostic criteria for MSA have several limitations. First, it is predominantly focused on the motor manifestations of the disease. However, both poorly levodopa-responsive parkinsonism and cerebellar ataxia are not rare conditions and actually occur more commonly in disorders other than MSA [14, 15]. Furthermore, although rare, even the combination of both can occur in other disorders [5, 16]. Second, autonomic failure, especially genitourinary dysfunction is not specific to MSA. It can occur in other neurodegenerative disorders and even in otherwise healthy individuals in their 50 and 60 s, which is a common onset age of MSA [2, 17, 18]. Indeed, it is estimated that the prevalence of urinary incontinence is 20–40 % in community-dwelling middle aged women and 7–24 % in men [19–21]. With this high prevalence in the general population, one can assume that a patient with parkinsonism or cerebellar ataxia with pathology other than MSA can coincidently develop urinary incontinence with a pathophysiology unrelated to motor symptoms, which will lead to overdiagnosis of MSA. Furthermore, current clinical diagnostic criteria do not consider the types of urinary incontinence such that the diagnosis of MSA can be made in a patient with any type of urinary incontinence despite the fact that urge incontinence and stress incontinence appear to have different pathophysiologies [22]. Another thing to mention is that there is no item for the female equivalent of male impotence, although reduced genital sensitivity has been suggested [13, 23]. Third, orthostatic hypotension can also be seen in many conditions other than MSA. The current guideline recommends that other causes of orthostatic hypotension should be excluded [12]. However, sometimes it is not easy to tell whether orthostatic hypotension in a patient is due to MSA or due to other causes. For example, one study showed that approximately 20 % of Parkinson Disease (PD) patients developed symptomatic orthostatic hypotension [24]. Furthermore, orthostatic hypotension can be observed even in healthy individuals. A study on community-dwelling elderly showed that 6.4 % of the otherwise healthy individuals had orthostatic hypotension with a decrease in systolic blood pressure greater than 20 mmHg, and 1.6 % had a decrease in systolic blood pressure greater than 30 mmHg [25]. Given that MSA is a rare disorder, this low prevalence of orthostatic hypotension in the general population can affect the specificity of the clinical diagnosis of MSA. Determining the presence of orthostatic hypotension is another problem. Sometimes a patient with a positive orthostatic hypotension test shows no orthostatic hypotension in a test performed several hours or days later and vice versa, which complicates the diagnosis. The meaning of 'significant orthostatic blood pressure decline that does not meet the level required in probable MSA' for the diagnosis of possible MSA is also not clear without

specifying the level of decrease in blood pressure. Fourth, both autonomic failure and motor symptoms are needed for the diagnosis, but it does not develop simultaneously in many patients. Some MSA patients develop only autonomic failure early in the course of the disease and are misdiagnosed as primary autonomic failure for years, whereas some other patients develop autonomic failure after as long as 15 years after disease onset delaying the correct diagnosis [9, 26].

Pathological diagnostic criteria

The histopathology of MSA encompasses four major features: (1) selective neuronal loss and axonal degeneration mainly involving the nigrostriatal and pontocerebellar systems; (2) four types of cellular α-synuclein (αSyn) immunoreactive inclusions [glial cytoplasmic inclusions(GCIs) within oligodendrocytes, less frequent glial nuclear inclusions (GNIs), neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs)] [27]; (3) astroglial cytoplasmic inclusions and threads of similar composition, and (4) myelin pallor and accompanying gliosis [28]. Because there are no specific markers for the clinical diagnosis of MSA, the definite diagnosis rests on the results of neuropathological examination. The histological hallmark is the presence of cytoplasmic αSyn positive GCIs within oligodendroglial cells, which is required for the postmortem diagnosis of definite MSA [4, 29]. However, pathological diagnostic criteria also bear some limitations.

There is evidence that PD and the parkinsonian variant of MSA (MSA-P) overlap at multiple levels [30]. Both disorders are characterized by deposition of abnormally phosphorylated fibrillar αSyn within the CNS suggesting shared pathophysiological mechanisms [31]. Whereas αSyn aggregates in MSA predominantly involve the cytoplasm of oligodendrocytes, in PD brains these aggregates (Lewy bodies and neurites) are found in neurons and axons [32, 33]. While the type, composition, and cellular distribution of the aggregates are clearly different [4, 33], there is still important pathological overlap [34]. In both disorders, neurodegeneration is associated with the Lewy body and GCI burden as well as an increase of soluble αSyn in substantia nigra and striatum [30], whereas no insoluble αSyn was found in MSA, a divergence from other synucleinopathies [35]. Apart from the overlap in degeneration of the dopaminergic nigrostriatal system, involvement of the autonomic nervous system including the dorsal motor vagal nucleus, autonomic parts of the spinal cord, and the peripheral autonomic nervous system (e.g. the cardiac and enteric systems) is common in both MSA-P and PD [34, 36–38].

Intriguingly, brainstem Lewy bodies—a classical hallmark of PD—were also reported in MSA [37, 39, 40], and, vice versa, GCI pathology occurred in familial PD cases with rapid disease progression [32, 41] whereas a study of 59 Japanese MSA cases did not find any concomitant Lewy pathology [42] that could reflect genetic or environmental differences to European patients. In the brain of an elderly patient diagnosed with PD, in addition to widespread Lewy pathology and moderate cell loss in substantia nigra, GCIs were found in multiple brain areas, suggesting a combination of PD and early stage of MSA that had not progressed to striatal involvement [43]. This association, termed "transitional variant," is of unknown clinical and pathological significance [44].

These findings suggest a continuum of changes rather than strictly divided entities [45], but the molecular basis and pathogenesis of these co-existing pathologies remain to be elucidated. Recently, in a British family with autosomal-dominant inheritance related to a G51D *SNCA* mutation, sharing features of both PD and MSA were reported [46], and in a Finish patient with a novel *SNCA* mutation A53E, PD-type pathology was associated with severe atypical MSA [47], both providing a possible link between the two disorders. These morphological similarities provide further evidence that αSyn aggregates are able to interfere with physiological processes thereby triggering neurodegenerative processes irrespective of the underlying inclusion pathology.

Diagnosis of MSA can be readily made without difficulty in some patients. However, for the reasons mentioned above, in some patients, it can be overdiagnosed, and in other patients, the diagnosis can be missed or delayed [33]. To this end, to improve the clinical diagnosis, current diagnostic criteria provides additional, supporting, and non-supporting features for the diagnosis (Tables 1, 2). Notwithstanding, the accuracy, especially the sensitivity of a clinical diagnosis of MSA, is still not high enough at 88.2 % when diagnosed by movement disorder specialists and 64.3 % when diagnosed by general neurologists [48, 49]. Furthermore, although many new pathological, clinical, and neuroimaging features which can improve the diagnosis of MSA have been described in recent studies, they are not considered in the current diagnostic criteria mostly because those studies were published after the publication of the current diagnostic criteria.

Investigations for improved diagnosis of MSA

In addition to MRI, single photon emission computed tomography (SPECT), and positron emission tomography (PET), which are included in the current diagnostic criteria, several investigations may help to improve the diagnosis of MSA in clinical practice [50]. However, the usefulness of these investigations and how much the findings from these

Table 2 Features supporting (red flags) and not supporting a diagnosis of MSA [12]

Supporting features
Orofacial dystonia
Disproportionate antecollis
Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)
Contractures of hands or feet
Inspiratory sighs
Severe dysphonia
Severe dysarthria
New or increased snoring
Cold hands and feet
Pathologic laughter or crying
Jerky, myoclonic postural/action tremor
Nonsupporting features
Classic pill-rolling rest tremor
Clinically significant neuropathy
Hallucinations not induced by drugs
Onset after age 75 years
Family history of ataxia or parkinsonism
Dementia (on DSM-IV)
White matter lesions suggesting multiple sclerosis

investigations improve the diagnosis should be scrutinized before they are recommended to clinicians. There are also neuroimaging studies using more investigational protocols which need specialized techniques or use of novel ligands which are not widely available. Several studies have analyzed samples from patients including plasma and cerebrospinal fluid which have revealed the distinguishing features of MSA. However, these methods will not be considered in this review because they are not readily available in clinical practice yet, and more studies are needed for those methods to be reliably applied to clinical practice.

MRI

Atrophy of the putamen, middle cerebellar peduncle, pons, or cerebellum on an MRI is included as an additional feature for the diagnosis of possible MSA in the current diagnostic criteria. In addition, several studies have shown that lateral slit-like hyperintense putaminal rim and putaminal hypointensity occur more often in MSA patients than in controls and PD patients on conventional brain MRIs [7, 51–55]. Slit-like hyperintense putaminal rim has been related to the enlargement of the intertissue space between the putamen and the external capsule and the tissue rarefaction associated with neuronal loss and gliosis [56, 57]. However, several studies have shown that the slit-like hyperintense rim is present in normal subjects on 3.0T MRIs [7, 58–60], and even on 1.5T MRIs [61], (Fig. 1), which is thought to be a truncation artifact or age-related disproportionate ferritin deposit between the lateral margin area and the remainder of the putamen. Thus, it is suggested that the discontinuity or irregular disruption of rim is a more reliable marker for MSA than the rim itself [7, 61]. Putaminal hypointensity is observed especially in the posterolateral region along with putaminal atrophy and may reflect diffuse ferritin and Fe^{3+} deposits [57]. It is more readily observed with imaging sequences sensitive to the susceptibility effect of mineral deposits. However, a recent study using 3.0T MRI showed that age-matched patients with PD and controls also presented putaminal hypointensity, which might have resulted from the increased susceptibility effect of 3.0T MRI [58]. A cruciform hyperintensity within the pons, referred to as a 'hot-cross bun' sign, was observed in 63 % of patients with MSA and 80 % of patients with MSA-cerebellar type (MSA-C) [62, 63]. However, this finding is not specific to MSA and can be observed in other diseases with pontocerebellar degeneration including spinocerebellar ataxia

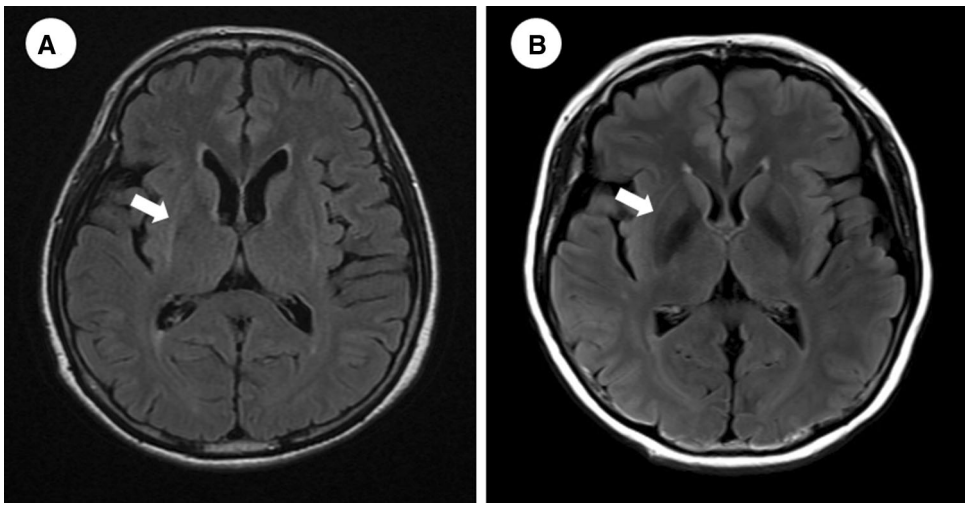

Fig. 1 Slit-like putaminal hyperintense rim (*arrows*) on fluid-attenuated inversion recovery images in a patient with MSA at 1.5T (**a**) and a normal subject at 3.0T (**b**)

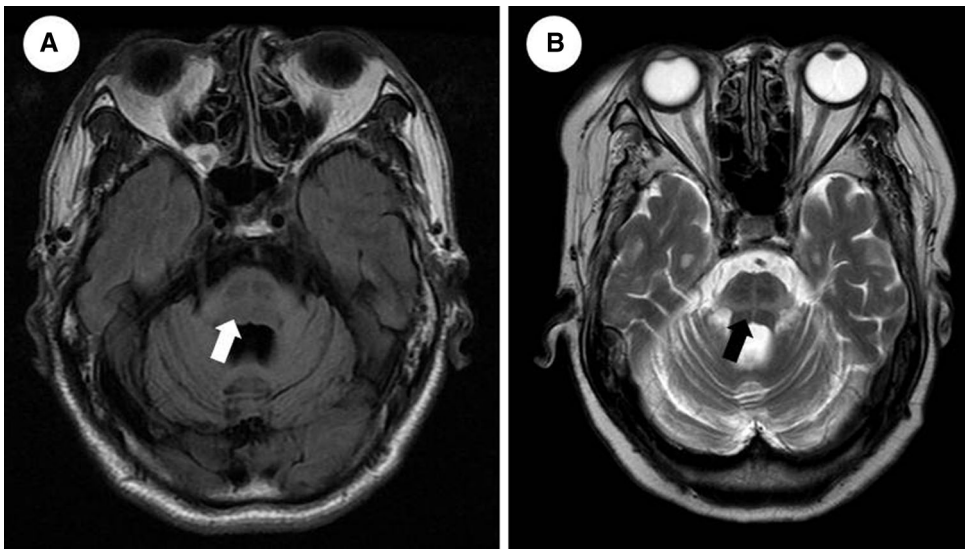

Fig. 2 'Hot cross bun' sign (*arrows*) in a patient with SCA17 (**a**) and a patients with bilateral pontine infarction (**b**) (Reproduced from Roh et al. [67] with kind permission of Journal of Movement Disorders)

(SCA), variant Creutzfeldt-Jakob disease, vasculitis-associated parkinsonism, cerebrotendinous xanthomatosis, and even after bilateral pontine infarction [64–67] (Fig. 2)

Functional brain imaging

Abnormalities in ^{18}F-2-fluoro-dexosy-D-glucose (FDG) PET and SPECT are included as an additional feature for the diagnosis of possible MSA in the current diagnostic criteria (Table 1). Previous studies have shown that FDG PET and perfusion SPECT could discriminate MSA-P from PD and MSA-C from other degenerative cerebellar ataxias by visual inspection [52]. However, the discrimination of MSA is not robust due to significant overlaps, and it needs to be evaluated whether these methods can reliably be used in patients with early MSA. Presynaptic dopaminergic imaging shows presynaptic nigrostriatal degeneration even in uncertain cases; however, it cannot discriminate MSA from other parkinsonian syndromes including PD and progressive supranuclear palsy (PSP) [68, 69]. Furthermore, some patients with MSA-C show normal dopamine transporter imaging [70].

Imaging of cardiac sympathetic innervation

^{123}I-metaiodobenzylguanidine (MIBG) is an analog of guanethidine, an adrenergic blocking agent, which is taken up and stored by sympathetic nerve endings through a mechanism similar to that of noradrenaline. Therefore, MIBG myocardial scintigraphy can assess the postganglionic presynaptic cardiac sympathetic nerve endings. In contrast to PD where cardiac MIBG uptake is reduced reflecting the degeneration of sympathetic axons in the heart, cardiac MIBG uptake was preserved in MSA in many studies, and it is claimed that MIBG myocardial scintigraphy can differentiated MSA from PD in the early stage of the disease [71, 72]. However, there is a significant overlap in MIBG uptake between PD and MSA, and some studies have shown reduced uptake in MSA [6, 73, 74]. Given the overlap and much higher prevalence of PD over MSA, its diagnostic value is limited.

Transcranial sonography

Transcranial B-mode sonography (TCS) is a relatively inexpensive, radiation-free, easily applicable technique to visualize parenchymal structures such as the substantia nigra and lenticular nucleus. Whereas approximately 90 % of PD patients present enlarged echogenicity of the substantia nigra, though not related to the disease duration or severity, 10–30 % of patients with atypical parkinsonism show an abnormality thus differentiating MSA from PD [52, 75, 76]. In addition, 70–90 % of patients with MSA or PSP present hyperechogenicity of the lenticular nucleus while it is observed in 23 % of PD patients [77, 78]. Based on these findings, it has been claimed that TCS can be used to discriminate between PD and atypical parkinsonism, and a recent study has demonstrated that this method shows accuracies comparable to FDG-PET for the differential diagnosis of other neurodegenerative parkinsonisms [79]. However, the major drawback of TCS in the diagnosis of MSA is its inability to differentiate MSA from other atypical parkinsonisms. Furthermore, there is a poor temporal window in about 10–15 % of the subjects, and the technique depends somewhat on the examiner's experience.

Sphincter electromyography

Anal sphincter electromyography (EMG) is a useful method for detecting the neurogenic change of the anal

sphincter muscle, which reflects the degeneration of Onuf's nucleus. Anal sphincter EMG has been reported to be useful in the differential diagnosis between MSA and PD [80] and was included as a diagnostic investigation in the 1st consensus criteria [81]. However, further studies have shown that anal sphincter EMG does not distinguish MSA from PD, and a negative test could not exclude a diagnosis of MSA, especially in the early stage of the disease [8, 82]. Thus, anal sphincter EMG was not included as a diagnostic investigation in the 2nd consensus criteria.

Quantitative autonomic function tests

Although various autonomic dysfunctions develop in patients with MSA, only orthostatic hypotension and urinary symptoms are included in the diagnostic criteria. However, as mentioned earlier, these autonomic symptoms can occur in other neurodegenerative disorders including PD, which hampers the diagnosis of MSA. In this regard, several standard quantitative autonomic tests including Valsalva maneuver, tilt table test, quantitative sudomotor axon reflex test, and thermoregulatory sweat test (TST) have been used to discriminate MSA from PD, and the results showed that none of these tests distinguished between MSA and PD, alone or in combination [83, 84]. However, recently, it has been claimed that TST combined with the composite autonomic scoring scale for laboratory quantification of generalized autonomic failure can be used for the differential diagnosis of MSA [6, 85].

Video oculography

The detection of subclinical cerebellar dysfunction in patients with parkinsonism would help the differential diagnosis of MSA. In this regard, clinical examination of extraocular movements with laboratory recordings may provide a useful adjunct. One study has shown that patients with MSA are characterized by excessive square wave jerk, hypometric saccades, impaired suppression of the vestibule-ocular reflex, and spontaneous nystagmus as well as positional downbeat nystagmus (pDBN) [86]. Another study has documented that the presence of perverted head-shaking nystagmus and pDBN may be a clue for the diagnosis of MSA [87]. However, no other studies have examined the usefulness of the examination of extraocular movement in the differential diagnosis of MSA, and thus, further studies are needed.

Boundary issues in the diagnosis of MSA

As discussed earlier, recent pathological and clinical studies have shown that MSA can have a wider range of presentations than previously thought. This makes the accurate diagnosis of MSA more difficult and expands the list of differential diagnoses. Among these, several issues need to be discussed in detail regarding the current diagnostic criteria.

Table 3 Overlapping and discriminating morphological features of MSA and PD

PD		MSA
Presynaptic terminals, axons, neurites (LN), Neurons (LB), dendrites, astroglia	**Aggregates**	Oligodendroglia (GCI), neurons (NCI), axons, astroglia
Content		
αSyn, ubiquitin, parkin, synphilin-1, NF proteins, actin, dorfin, MAPs, tau, 14-3-3, P25α (others different)		
Distribution / neurodegeneration		
Multisystemic: CNS, PNS, autonomic NS brunt. SN, striatum ← soluble αSyn → brunt. SN, striatum (MSA-P)		
SN: αSyn density; neuron loss +	**Correlations**	αSyn –, GCI density –, neuron loss +
Synaptopathy–axonopathy → neuron degeneration	**Primary lesion**	Oligodendropathy → demyelination, axonopathy → neuron loss
LBs, LNs, no GCIs	**Association**	LBs + GCIs (10–28%)
Synopsis		
Molecular/morphologic overlaps suggest a continuum of lesions rather than distinct entities with similar mechanisms of neurodegeneration, but the etiology of both is poorly understood.		

Neuropathological Issues

Overlapping and distinguishing features between MSA-P and PD are shown in Table 3.

Despite a rare co-occurrence of MSA with PSP, a four-repeat tauopathy morphologically featured by tufted astrocytes, tau-positive neuronal and oligodendroglial inclusions [88], four cases showing both pathologies were published [89–91]. The cerebellar phenotype of PSP Richardson's syndrome [92, 93] and genetic or secondary late-onset ataxias may be labeled as MSA-C, because of similar disease presentation [94], but they show different neuropathologies.

Neuropathological examination of a male aged 74 years with a clinical diagnosis of "probable MSA-C" showed MSA-C with pronounced β-amyloid pathology in the frontal lobe and mild hippocampal tau pathology [95], but concomitant AD-like pathologies in MSA are less frequent than those in age-matched controls [39]. Recently, two patients aged 71 and 72 years were reported to show combined MSA and mild AD (Braak neuritic stages III and IV), with abundant αSyn-positive GCIs and NCIs and co-occurrence of αSyn and tau pathology in hippocampus and entorhinal cortex. Immunoreactivity for p62, a ubiquitin–proteasome system-related protein, and UBB+1, a mutant form of ubiquitin and marker for proteasomal dysfunction, was found in most tangles, but only in few αSyn-positive inclusions, suggesting that the proteasomal pathways differ between αSyn and p-tau-bearing neurons [96].

Sporadic adult-onset ataxia of unknown etiology

Sporadic adult-onset ataxia of unknown etiology (SAOA), also called idiopathic adult-onset cerebellar ataxia, constitutes the most common progressive ataxias in adults. SAOA starts at the age of 50–55 years which is slightly lower than that of 55–60 years in MSA [97, 98]. The diagnosis of SAOA is made after excluding known causes of ataxias [14]. Probably, it is a heterogeneous group of diseases with various etiologies including genetic, inflammatory, immunologic, and metabolic factors. MSA-C can be indistinguishable from SAOA in the early stage when the patient has only cerebellar symptoms. Given that SAOA has much more benign course [98, 99], an early accurate diagnosis has important clinical consequences. However, in a patient with recently developed progressive ataxia, one can rarely predict whether the patient will remain in SAOA or will later develop autonomic failure and evolve to MSA. Sometimes, the presence of mild parkinsonism helps the diagnosis, but this is not usual. In this scenario, early MSA can be misdiagnosed as SAOA. Indeed, one study has shown that 24 % of patients diagnosed with SAOA evolved to MSA in 5 years [99]. Conversely, a patient with SAOA can be misdiagnosed as having MSA when the patient develops urinary dysfunction or orthostatic hypotension due to other causes.

SCAs and other genetic disorders

SCA refers to a group of autosomal dominant genetic disorders characterized by progressive neurodegeneration of the cerebellum and its efferent and afferent connections. The presence of a family history of cerebellar ataxia usually helps the diagnosis of SCA; however, a significant proportion of patients with SCA do not have a family history with the frequency of patients with the SCA mutation being 9–22 % among patients with apparently sporadic cerebellar ataxia [100–102]. Both MSA-C and SCA present with cerebellar ataxia; thus, when a patient with apparently sporadic SCA develops autonomic failure in addition to cerebellar ataxia, this patient can be misdiagnosed with MSA-C. Furthermore, some SCAs including SCA 2, 3, 6, and 17, and dentatorubropallidoluysian atrophy develop parkinsonism with nigrostriatal degeneration evidenced by abnormal dopamine transporter imaging [103, 104], sometimes even without cerebellar dysfunctions, which can be misdiagnosed as MSA-P when accompanied by autonomic failure. In agreement with this, a recent study showed that mutations in the SCA genes were found in 7.3 % of the patients who met the clinical diagnostic criteria for MSA [5], suggesting that genetic testing for SCAs should be included in the diagnostic workup for MSA. Of note is that there are reports on Lewy bodies or αSyn-positive GCIs in patients with SCA [105–107], suggesting a relationship between SCA mutations and α–synucleinopathies.

There are other genetic disorders which can clinically mimic MSA. Among them are fragile X tremor/ataxia syndrome, Friedreich ataxia, Perry syndrome, hereditary spastic paraplegia, mitochondrial disorders, and other autosomal recessive cerebellar ataxias [108, 109]. *SNCA* multiplications also can lead to pathological and clinical features of MSA as well as PD and dementia with Lewy bodies (DLB) [41].

Familial MSA

Multiple system atrophyis considered a sporadic disorder, and a family history of ataxia or parkinsonism is defined as a non-supporting feature in the current diagnostic criteria. However, familial aggregation of parkinsonism has been reported in MSA [110, 111], and there are reports on autopsy-proven familial MSA [11, 112, 113]. Based upon these, a recent Japanese study showed that *COQ2* is a causative gene as well as a risk gene for familial and sporadic MSA [112]. However, this finding has not been

replicated in other ethnic groups, and the role of *COQ2* in the pathogenesis of MSA is still questionable [114–116].

MSA and dementia

Despite mild cognitive dysfunction being repeatedly described in patients with MSA [117–119], dementia is defined as a non-supporting feature in the current diagnostic criteria. However, dementia as well as mild cognitive dysfunction has been reported in patients with autopsy-proven MSA [39, 120], and recent reports have shown that dementia occurs in up to 31 % of MSA patients [10], which indicates that the diagnosis of MSA cannot be excluded by the presence of dementia. The structural correlates of cognitive decline in MSA are still unclear, because a recent clinicopathological study of nine MSA cases each with and without cognitive impairment found no essential qualitative and quantitative differences in MSA-specific αSyn, GCI density and distribution, or secondary pathological conditions such as concomitant Alzheimer-related pathology, cerebral amyloid angiopathy or cerebrovascular disease between the two groups [121]. In a clinicopathological study of 44 MSA patients, four (aged 65–72 years) with mild memory disturbances and frontal executive dysfunctions scored Braak neuritic stage III or IV with variable amounts of cortical amyloid plaques. One demented woman aged 82 years showed MSA-P with fully developed AD (Braak stage V; NIA-AA ABC score 3/3/3) and severe amyloid deposits in the whole cortex, while the brain of a demented male aged 55 years with MSA-C showed no AD-related or any other concomitant cerebral lesions. The GCI load in striatum and the proportion of cases with subcortical small vessel disease did not significantly differ between MSA cases with and without dementia [39]. In view of limited data on the molecular basis of cognitive and behavioral disorders in MSA, currently related to slowly progressive striatofrontal deafferentation [10, 122] or other subcorticocortical lesions which occasionally may spread to the cortex, further studies on morphological substrates of the increasingly observed cognitive impairment in MSA are warranted.

The presence of dementia in MSA, especially in MSA-P, may pose a problem in the diagnosis of DLB. MSA-P and DLB are different diseases with different pathologies; however, both diseases share poorly levodopa-responsive parkinsonism and autonomic failure [123]. According to the current diagnostic criteria, the most obvious feature distinguishing DLB from MSA-P is the presence of dementia with fluctuating cognition and visual hallucinations. Given that dementia occurs in patients with MSA and that even visual hallucination occurs in a small proportion of patients with MSA [18, 124, 125], it will be difficult to make a diagnosis between DLB and MSA-P when a patient presents with parkinsonism, dementia, and autonomic dysfunction without cerebellar symptoms. Furthermore, there is overlap in the cognitive profiles of DLB and MSA although more profound in DLB [124]. Fluctuating cognition may help the diagnosis because it appears to be absent in MSA [123]. However, as it has been suggested, this feature may have been overlooked in MSA [10]. Further studies are needed to improve the accuracy of the differential diagnosis between these two diseases.

MSA with normal dopamine transporter imaging

Neuropathology of MSA involves both presynaptic nigrostriatal and postsynaptic striatal neurons in patients with parkinsonism and even in patients with MSA-C without overt parkinsonism. Dopamine transporter imaging readily shows presynaptic nigrostriatal degeneration in these patients. However, recently, there have been two reports on normal dopamine transporter imaging after 3 and 10 years of parkinsonism, respectively, in autopsy-proven MSA-P patients [126, 127]. The authors suggested that there might have been postsynaptic-only striatal pathology at the time of the imaging, and the presynaptic pathology developed later. These findings are different from that of scan without evidence of dopaminergic deficiency (SWEDD) in PD, in that MSA was pathologically proven in these patients. Given that dopamine transporter imaging is performed in less than 20 % of patients with MSA [18] and now it is becoming more available, it is possible that more MSA cases with normal dopamine transporter imaging will be found.

Prolonged survival in MSA

Multiple system atrophy is a rapidly and relentlessly progressing disorder with a mean survival of 6–10 years. However, recent reports have shown that 2–3 % of MSA patients have a prolonged survival of 15 years or more [9, 26]. Most, if not all, of these patients had similar disease courses with a slow progression of parkinsonism resembling PD in the first 10 years of disease and a subsequent rapid deterioration after the development of autonomic failure. Patients like this may well be diagnosed with PD before they develop autonomic failure, which shows the difficulty in making an accurate diagnosis of MSA. Of note, many of these patients develop motor fluctuations and levodopa-induced generalized choreic dyskinesias, which may lead to deep brain stimulation which should not be done in patients with MSA [128]. These rare cases of MSA-P with slow progression and prolonged survival were considered as "benign" forms [9], whereas another case with prolonged clinical course of 18 years showed extensive distribution of GCIs in CNS [129]. A non-motor

Table 4 A summary of the recent clinical, pathological, and laboratory findings to be considered in future clinical and pathological diagnostic criteria

Clinical
Combination of parkinsonism and cerebellar ataxia can occur in other diseases
Autonomic dysfunction (orthostatic hypotension and/or genitourinary dysfunction) is frequent in but not specific to MSA
Detailed protocol to determine the presence of orthostatic hypotension is not provided
Types of urinary incontinence are not considered
Onset of autonomic dysfunction can be delayed as long as 15 years
Familial MSA is reported rarely
Patients with MSA may develop cognitive decline and dementia
Pathologial
Pathological overlap between PD and MSA may be present
Some cases show co-exiting pathologies: Lewy body, tau, β-amyloid
Minimal change MSA
Incidental MSA
Laboratory
Putaminal hypointensity on brain MRI in MSA-P
MIBG scan, video oculography, and TCS can help differentiate MSA from PD
Quantitative autonomic function test can help diagnose MSA
Mutations in the SCA genes were found in some patients presenting as MSA
COQ2 is reported as a causative gene as well as a risk gene for familial and sporadic MSA
MSA-P with normal DAT were reported

MSA multiple system atrophy, *PD* Parkinson disease, *DAT* dopamine transporter, *MIBG* ^{123}I-metaiodobenzylguanidine, *TCS* transcranial sonography, *SCA* spinocerebellar ataxia

variant of pathologically confirmed MSA showed no overt parkinsonism nor cerebellar symptoms [130].

'Minimal change' MSA

Rare cases of "minimal change" MSA-P showing GCIs and degeneration almost restricted to substantia nigra and putamen, thus representing "pure" striatonigral degeneration [62, 131–135], suggest that GCI formation is an early event and may be responsible for some of the clinical symptoms. One patient with preclinical MSA-C showed widespread GCIs, whereas NCIs and NNIs restricted to pontine basis, cerebellar vermis, and inferior olivary nuclei were associated with neuronal loss, suggesting a common link between these two lesions in early stages of the disease [136]. This case showing only mild clinical symptoms was recently suggested to represent "early MSA", rather than "minimal change" MSA [137]. Coexistence of sporadic Creutzfeldt-Jakob disease with "minimal change" MSA was recently reported in a Spanish woman aged 64 years [138].

Postmortem detection of MSA pathology in neurologically normal individuals ("prodromal/preclinical MSA") is extremely rare [132, 134]. They showed GCIs which were limited to the pons and inferior olivary nuclei, whereas neuronal loss was restricted to substantia nigra. The presence of GCIs may represent an age-related phenomenon, not necessarily progressing to over neuronal disease. These rare cases could be classified as "incidental MSA", similar to incidental Lewy body disease [139].

Conclusion

Multiple system atrophy is a rapid progressive disorder with no effective treatment, and its accurate diagnosis is important for the proper management of patients, especially in the early course of the disease when the disease is not fully developed yet. However, the current clinical diagnostic criteria have some limitations regarding early diagnosis, and it does not include recent clinical and laboratory findings which may improve the diagnosis. Similarly, the current pathological diagnostic criteria for MSA do not capture the recent findings in neuropathology. These aspects should be taken into consideration when revising the current diagnostic criteria (Table 4). This is especially true given that disease-modifying treatments for MSA are under investigation, and including patients with relevant pathology in an early phase of the disease as much as possible is of utmost importance.

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Conflicts of interest None.

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