A Guide for the Differential Diagnosis of Multiple System Atrophy in Clinical Practice

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Accepted 11 August 2022
Pre-press 30 August 2022

Abstract. Multiple system atrophy (MSA) is a sporadic and progressive neurodegenerative disorder with a complex differential diagnosis. A range of disorders—also of nondegenerative etiology—can mimic MSA, expanding its differential diagnosis. Both misdiagnosis and diagnostic delays are relatively common in clinical practice. A correct diagnosis is vital for daily clinical practice, in order to facilitate proper counselling and to timely install therapies in treatable disorders that mimic MSA. A correct diagnosis is also essential for including properly classified individuals into research studies that aim to better understand the pathophysiology of MSA, to develop specific biomarkers or to evaluate novel symptomatic or disease-modifying therapies. Here, we offer some practical guidance to support the diagnostic process, by highlighting conditions that may be considered as MSA lookalikes, by emphasizing some key clinical aspects of these mimics, and by discussing several useful ancillary diagnostic tests.

Keywords: Differential diagnosis, mimics, multiple system atrophy, neurodegenerative diseases

INTRODUCTION OF THE CLINICAL DILEMMA

Multiple system atrophy (MSA) is a sporadic, adult-onset, progressive neurodegenerative disorder, which is typically included in the overall category of so-called atypical parkinsonisms [1, 2]. MSA variably combines parkinsonism, cerebellar ataxia, dysautonomia, and corticospinal degeneration as its main features [2–4]. Usually, the condition progresses quicker than Parkinson’s disease (PD), with a mean survival of only 6–10 years [3]. The recently published diagnostic criteria of MSA present four levels of diagnostic certainty: neuropathologically established MSA (replacing the category of definite MSA), clinically established MSA, clinically probable MSA, and possible prodromal MSA [2].

At present, brain magnetic resonance imaging markers suggestive of MSA are mandatory for clinically established MSA (replacing the category of definite MSA), clinically established MSA, clinically probable MSA, and possible prodromal MSA [2]. However, due to the absence of specific and well-established disease biomarkers at this time, the diagnostic criteria still largely consist of clinical features, with the addition of some neuroimaging characteristics proposed both in 2008 and 2022 diagnostic criteria (MRI, FDG-PET, SPECT) [2, 5]. Nevertheless, establishing a
reliable diagnosis of MSA in clinical practice is commonly challenging, considering that its core features, such as levodopa-refractory parkinsonism and cerebellar ataxia, are shared by several other neurologic diseases. Additionally, not all main disease characteristics develop simultaneously, increasing the risk of a misdiagnosis in early disease stages, and thereby delaying a correct MSA diagnosis [2–4]. Indeed, our precision of establishing a clinical diagnosis of MSA is still disappointing. Two recent studies revealed a diagnostic accuracy of about 62–79% in referral autopsy series of patients with an antemortem diagnosis of MSA [4, 6].

In this paper, we will highlight several potential MSA mimics that may be included in its differential diagnosis, focusing on recognizable clinical aspects and on ancillary investigations that may be useful.

**MSA Diagnostic Criteria and Differential Diagnosis**

Using Table 1 as a starting point for our review, we intend to try and simplify the MSA differential diagnostic process, by summarizing the clinical presentations and possibly useful diagnostic tests that may be requested in order to establish a more accurate diagnosis in an earlier disease phase.

In Table 2, we share a brief overview of the newly published diagnostic criteria of MSA.

Considering the particular feature of orofacial dystonia (OFD) in MSA patients, an interesting recent study [7] analyzed videogrips of 24 MSA patients. OFD was mostly identified in MSA-P patients (85.71%), and oromandibular dystonia (OMD) was rarely recognized alone, with the jaw-closing type having been identified in all OMD patients. The most common combination was OMD with upper facial dystonia, blepharospasm and platysma dystonia. On average, OFD began 1.7 (SD = 0.5) years after the first symptom and 1.1 years (SD = 0.4) after levodopa treatment. Patients with OFD were treated with a significantly higher levodopa equivalent daily dosage (LEDD) ($p = 0.02$), compared to those without. This study concluded that OFD may be a manifestation of motor fluctuations in MSA [7].

MRI markers are necessary for clinically established MSA, which are summarized in Table 2 [2]. Contrary to the previous 2008 diagnostic criteria, where abnormal FDG-PET findings (hypometabolism of putamen, brainstem, or cerebellum) and presynaptic nigrostriatal dopaminergic denervation on SPECT or PET scans were included as additional features of possible MSA [5], in most recent criteria FDG-PET markers are referred to as supportive biomarkers for MSA diagnosis, as are polysomnography-proven REM-sleep behavior disorder, cardiac $^{123}$I-MIBG-scintigraphy, supine plasma norepinephrine levels, urodynamic testing, and pelvic floor neurophysiology [2]. Other proposed supportive biomarkers such as $\alpha$-synuclein oligomers in cerebrospinal fluid (CSF) and neurofilament light chain in CSF and plasma are less applicable in everyday clinical practice [2].

The great diversity in possible presentations commonly leads to diagnostic difficulties, and this issue is further compounded by the fact that available ancillary tests often do not provide more diagnostic certainty. A group of non-supporting features that argue against MSA has also been defined, which are briefly detailed in Table 2 [2] and may be important clues to consider potential MSA lookalikes. These factors are all important to consider. For example, in some relevant MSA mimics, such as spinocerebellar ataxia (SCA), family history is a key element [8, 9], even more so in cases with a relatively earlier onset. Therefore, a positive family history would argue against MSA, but importantly, a negative family history does not exclude the possible presence of genetically defined mimics of MSA. Other features may also be red flags that argue relatively against MSA, such as an exceedingly rapid disease course over weeks/months, as occurs in a paraneoplastic syndrome. This is usually associated with other neurological manifestations that are less suggestive of MSA, i.e., seizures, encephalopathy or neuronopathy. This category is of uttermost importance since it is tumor-associated, which mandates a swift screening, diagnosis, and treatment initiation. Tumor treatment might ameliorate the paraneoplastic syndrome, combined with immunotherapy and other symptomatic therapies when needed [10–14].

Below, we elaborate briefly on neuronal antibody-mediated diseases. Knowledge about their pathophysiology, clinical manifestations, and treatment have grown significantly over the past decade. This group of diseases sparks particular interest due to their frequent presentation with movement disorders and misdiagnosis as neurodegenerative conditions. Considering their potential response to treatment, a correct diagnosis must not be delayed [13]. Still, the actual frequency of these antibodies in patients who have an MSA-like presentation is yet to be determined.
| Etiology | Differential diagnosis | Mimic of MSA/C | Important clinical information | Complementary diagnostic methods |
|----------|------------------------|----------------|--------------------------------|---------------------------------|
| Genetic  | SCAs                   | Both           | Overlap MSA-c and SCA: progressive cerebellar ataxia, scanning dysarthria and/or oculomotor dysfunction Overlap MSA-p and SCA: parkinsonism, sometimes without cerebellar ataxia at onset Both: dysphagia; dystonia; autonomic dysfunction; RBD; pyramidal signs | Genetic testing |
|          | 1, 3, 7, 17            | MSA-c          | Red flags: family history, cognitive impairment, peripheral neuropathy, seizures, visual loss (retinal disease) |                                  |
|          | 2, 6                   | MSA-p          | (Continued)                      |                                  |
|          | 12                     | Both           |                                  |                                  |
|          | [3, 8]                 |                |                                  |                                  |
|          | DRPLA                  | MSA-c          | Overlapping features: cerebellar ataxia (may be only symptom at presentation) ± choreoathetosis ± myoclonus Red flags: epilepsy ± dementia; dementia may occur later on; extrapyramidal symptoms are rare | Genetic testing |
|          | [8, 9, 26]             |                |                                  |                                  |
|          | FXTAS [20]             | Both, mostly   | Older men (>50 y) Overlapping features: Classic FXTAS - intention tremor + ataxia Other mimicking features - parkinsonism ± postural/kinetic tremor ± autonomic dysfunction Tremor is not always present! Red flags: early cognitive dysfunction, clinically evident peripheral neuropathy, family history of primary ovarian failure or mental retardation | Genetic testing |
|          |                        | MSA-c          |                                  | Brain MRI (FXTAS: hyperintense lesions in MCP and splenium of corpus callosum T2/FLAIR) Abnormal DAT-scan does not exclude FXTAS! |
|          |                        |                |                                  |                                  |
|          | SPG7 [27, 28]          | MSA-c          | Later AO vs. other HSPs, mostly AR Overlapping features: cerebellar ataxia and mixed dysarthria ± nystagmus ± dysphagia ± urinary symptoms ± pyramidal signs Red flags: family history, progressive external ophthalmoplegia, visual loss, proximal weakness, mild lower limb spasticity, peripheral neuropathy | Genetic testing |
|          |                        |                |                                  |                                  |
|          | CANVAS (RFC1 gene)     | MSA-c          | Possible cause of late-onset ataxia Overlapping features: autonomic dysfunction (including OH); cerebellar ataxia and scanning dysarthric speech, cerebellar oculomotor abnormalities, brisk reflexes, parkinsonism Red flags: dry spasmodic cough, vestibulopathy, sensory neuropathy, prolonged disease course (CANVAS); absence of RBD, brainstem atrophy on brain MRI (suggestive of MSA-c) | Genetic testing for RFC1 EMG Video-oculography, videonystagmography |
|          | [29–34]                |                |                                  |                                  |
|          | Mitochondrial disorders [20, 35–37] | Both | Variable AO Overlapping features: may present/progress with parkinsonism and/or ataxia (frequent manifestation) with prolonged disease course Ataxia may be cerebellar, spinocerebellar or sensory Red flags: many other concomitant neurologic and/or systemic manifestations with broad phenotypic heterogeneity (neuropathy, myopathy, epilepsy, cognitive impairment, migraine, retinopathy, optic neuropathy, deafness, cardiomyopathy, diabetes) | Mitochondrial DNA studies (NGS) / nuclear DNA testing (NGS/whole exome sequencing) Muscle biopsy, EMG Metabolic evaluation (lactate and pyruvate, lactate/pyruvate ratio, serum aminoacids, acylcarnitine, urine organic acids, CSF lactate, pyruvate, aminooxids, 5-methyltetrahydrofololate) Cardiac evaluation EEG, neuroimaging |
|          |                        |                | (Continued)                      |                                  |
| Etiology              | Differential diagnosis | Mimic of MSAc/ MSAp/Both | Important clinical information (Overlapping features between differentials and red flags against MSA) | Complementary diagnostic methods |
|-----------------------|------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Neurodegenerative     | PD [3, 38]             | MSA-p                     | Overlapping features: parkinsonism ± dysautonomia ± postural instability
Red flags: slower disease progression, absent cerebellar involvement and pyramidal signs, asymmetric parkinsonism, good LDOPA response, motor complications and/or fluctuations associated with LDOPA treatment
More likely misdiagnosis: PD subgroup with early dysautonomia ± postural instability, moderate LDOPA response | No laboratory/imaging studies are accurate enough to differentiate
Supportive features:
Brain MRI
MIBG myocardial scintigraphy |
| PSP [3, 39]           | MSA-p                  | Overlapping features: poor LDOPA response, axial symptoms, early postural instability with falls, dysarthria, dysphagia
Red flags: less frequent true autonomic dysfunction; supranuclear vertical gaze palsy (may be absent at PSP-p’s initial stages?); frontal cognitive dysfunction; ataxia is not usually a prominent symptom | No laboratory/imaging studies are accurate enough to differentiate
Supportive features:
Brain MRI
FDG-PET |
| DLB [3, 40]           | MSA-p                  | Overlapping features: poorly LDOPA-responsive parkinsonism ± autonomic dysfunction ± RBD ± repeated falls
Red flags: cognitive decline with dementia, fluctuating cognition, visual hallucinations (hallucinations in nonvisual modalities may coexist), delusions, absent cerebellar symptoms | No diagnostic biomarkers available
Supportive of diagnosis:
Brain MRI
FDG-PET
MIBG myocardial scintigraphy |
| Corticobasal degeneration [41] | MSA-p | Overlapping features: LDOPA-resistant parkinsonism ± limb dystonia ± myoclonus ± abnormal gait ± falls ± postural instability ± corticospinal signs
Red flags: asymmetric parkinsonism, early cognitive dysfunction (including apraxia, executive and visuoperceptual dysfunction, aphasia), behavioral changes, cortical sensory loss, alien limb phenomena, oculomotor apraxia | No established disease biomarkers
Supportive features:
Brain MRI
FDG-PET |
| Sporadic adult-onset ataxia of unknown etiology [3, 42, 43] | MSA-c | Overlapping features: cerebellar symptoms ± corticospinal signs ± mild urinary symptoms
Red flags: sensory disturbances; slower disease progression; severe autonomic failure is rare and may appear many years after ataxia onset | Exclusion diagnosis
Brain MRI (isolated cerebellar atrophy)
Genetic tests for common genetic ataxias |
| Primary autonomic failure [44] | Both | Overlapping features: OH/syncope in midlife or later; genitourinary, bowel, and/or thermoregulatory dysfunction; RBD
Red flags: no evidence of CNS dysfunction other than RBD; slower disease progression
Increasing awareness of progression to other synucleinopathies (MSA, PD, or DLB) | Q­SART (abnormal in PAF), thermoregulatory sweat test (if altered + normal Q­SART: higher risk of progression to MSA)
Cardiac functional imaging (SPECT/PET) – altered in PAF, normal in MSA
Brain MRI
Bloodwork: supine/orthostatic norepinephrine levels (low in PAF) | (Continued) |
| Etiology                   | Differential diagnosis | Mimic of MSAc/MSAp/Both | Important clinical information                                                                                                                                                                                                 | Complementary diagnostic methods |
|---------------------------|------------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Paraneoplastic syndromes | Anti-Hu [11–13]        | MSA-c                   | Overlapping features: autonomic failure (gastrointestinal pseudo-obstruction, OH, urinary tract dysfunction), subacute cerebellar degeneration, dysphagia, focal and segmental dystonia, chorea; rapid progression
Red flags: cognitive dysfunction, seizures (including epilepsy partialis continua), opsoclonus-myoclonus syndrome, retinopathy, sensorineuronal hearing loss, sensitive neuropathy, brain MRI abnormalities | CSF analysis, brain MRI Thoracic-abdominal- pelvic CT |
|                           | Anti-Yo and Tr [10, 12, 13] | MSA-c                   | Overlapping features: cerebellar syndrome
Red flags: peripheral neuropathy, encepalopathy; most often isolated cerebellar ataxia                                                                                                                                                    | Scrotal/endovaginal + thyroid ultrasound, mammography Upper endoscopy and colonoscopy Neuronal autoantibodies (serum and/or CSF) Bloodwork (including lymphoma study, β-HCG, AFP, CA-125) Consider FDG-PET |
| Anti-amphiphysin          | [13, 14]               | MSA-c                   | Overlapping features: cerebellar ataxia; brain MRI mimic (hot cross bun sign)
Red flags: cognitive dysfunction (limbic encephalitis), sensory ganglionopathy and myelopathy, SPS                                                                                                                                            |                                                                                 |
| Neuronal antibody mediated diseases | Anti-CASPR2 [12, 13] | Both                    | Overlapping features: autonomic dysfunction, cerebellar ataxia, parkinsonism, tremor, myoclonus, sleep dysfunction, chorea
Red flags: associated signs – cognitive dysfunction, seizures, neuromyotonia, possible paroxysmal/episodic presentation of ataxia, weight loss                                                                                                             |                                                                                 |
| Anti-LGI1 [13]            | MSA-p                  | Both                    | Overlapping features: autonomic dysfunction, parkinsonism, tremor, chorea, rare myoclonus
Red flags: cognitive dysfunction, (faciobrachial) seizures, hyponatremia (associated with seizures ± movement disorders ± altered mental status/cognitive dysfunction de novo)                                                                                     |                                                                                 |
| DPPX [13]                 | Both                   | Both                    | Overlapping features: cerebellar ataxia, dysautonomia, parkinsonism, tremor, pyramidal signs, myoclonus
Red flags: cognitive dysfunction, hyperekplexia, SPS, sensory symptoms, prolonged diarrhea, weight loss                                                                                                                                 |                                                                                 |
| IgLON5 [13]               | Both                   | Both                    | Overlapping features: cerebellar ataxia, parkinsonism, myoclonus, sleep disorder, bulbar dysfunction, gait abnormalities, chorea, rarely dystonia
Red flags: cognitive decline, eye movement abnormalities (non-cerebellar, e.g.: vertical gaze palsy)                                                                                                                                               |                                                                                 |
Table 1 (Continued)

| Etiology            | Differential Diagnosis | Mimic of MSAc/MSApl/Both | Important Clinical Information (Overlapping features between differentials and red flags against MSA) | Complementary Diagnostic Methods |
|---------------------|------------------------|--------------------------|-----------------------------------------------------------------------------------------------|----------------------------------|
| Anti-GAD ataxia     | MSA-c                  |                          | Overlapping features: truncal and gait predominant ataxia, nystagmus, dysarthria, myoclonus, pyramidal signs, dysautonomia, dystonia. Red flags: subacute/slowly progressive clinical course; often coexists with AI diseases; cognitive dysfunction (limbic encephalitis); overlap with SPS; refractory epilepsy; sensory symptoms; typically, women, 50–60 y. |                                |
| Immune/inflammatory | Gluten ataxia [45]     | MSA-c                    | Overlapping features: similar ON (±53 y); cerebellar ataxia ± myoclonus ± chorea. Red flags: peripheral neuropathy ± myopathy ± myelopathy ± cognitive impairment ± psychiatric symptoms. | Brain MRI Anti-gliadin and/or anti-transglutaminase antibodies |
| MS [46]             | MSA-c                  |                          | Overlapping features: oculomotor abnormalities ± scanning dysarthria ± intention tremor ± cerebellar ataxia ± dysautonomia ± urinary abnormalities ± corticospinal signs. Primary progressive cases may have later ON; cerebellar symptoms are very prevalent in these patients. Red flags: mean ON ± 30 y, relapsing-remitting course more common, with accumulated disability; visual, motor and/or sensory symptoms frequently coexist; brain MRI abnormalities; if progressive disease, slow clinical deterioration with coexisting neurological symptoms (often located to spinal cord lesions). | Brain MRI with WML suggesting MS CSF |
| Others              | HIV infection [47]     | MSA-c                    | Overlapping features: sporadic progressive pure cerebellar ataxia, dysarthria, cerebellar oculomotor dysfunction, intentional tremor, dysdiadochokinesia. Rare! But should be excluded – treatable. Red flags: slower progression, risk factors for HIV, history of or coexisting HIV-associated infections/malignancies, brain MRI with cerebellar atrophy. | HIV serology CSF workup Brain MRI |
| Vascular parkinsonism | Both, mostly MSA-p      |                          | Overlapping features: symmetrical parkinsonism; poor LDOPA response; mixed speech changes; gait abnormalities, including FOG with shuffling steps and falls; postural instability; autonomic dysfunction with OH, urinary incontinence, sudomotor dysfunction; pyramidal signs; possible MRI mimicry with putamen hypointensities. Red flags: classic predominant lower-body parkinsonism with milder upper limb signs; rare cerebellar signs; cognitive impairment/dementia; relevant cerebrovascular disease on neuroimaging. | Clinical history with cardiovascular risk factors, look out for systemic vascular disease complications Brain MRI with considerable small vessel disease (WML), previous strokes (basal ganglia or cerebellum). |

(Continued)
Table 1 (Continued)

| Etiology                        | Differential diagnosis | Mimic of MSAc/MSAp/Both | Important clinical information                                                                 | Complementary diagnostic methods                                                                 |
|---------------------------------|-------------------------|--------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Normal pressure hydrocephalus [51] | MSA-p                   | Overlapping features: parkinsonian gait, gait initiation failure, small and shuffling steps, difficulty turning and multistep turns, festination, falls; postural instability; urinary urgency, difficulty inhibiting bladder emptying, nighttime urinary frequency | Red flags: frontal-subcortical cognitive dysfunction  
Not all 3 classic triad symptoms need be present!  
Gait/balance disturbance + at least 1 other impairment (cognition/urinary symptoms) | Neuroimaging: pathologically enlarged ventricular size not due to cerebral atrophy/congenital enlargement (Evans index >0.3), without macroscopic obstruction to CSF flow  
Evacuating LP with normal opening pressure; clinical improvement |
| Prion diseases [20, 52, 53]     | Both                    | Overlapping features: movement disorders may be initial manifestation or only symptom  
Subacute cerebellar ataxia ± extrapyramidal disorder (parkinsonism, dystonia, choreoathetosis, tremor, hemiballismus) and pyramidal signs ± postural instability ± myoclonus ± dysautonomia ± sleep disturbances  
Previous description of atypical parkinsonism-like syndromes (mostly PSP, CBD) | Red flags: quick progression, rapid mental deterioration with dementia, kinetic mutism, visual disturbances, gait-palsy, substantial heterogeneity of clinical presentation and its evolution | Brain MRI  
EEG, CSF |

Ab, antibodies; AD, autosomal dominant; AFP, alpha-fetoprotein; AR, autosomal recessive; AI, autoimmune; AO, age of onset; BP, blood pressure; CA-125, cancer antigen 125; CANVAS, cerebellar ataxia with neuropathy and vestibular areflexia syndrome; CASPR2, Contactin-associated-protein-2; CBS, corticobasal syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DaTSCAN, dopamine transporter scan; DLT, dementia with Lewy bodies; DPPX, Dipeptidyl-peptidase-like protein-6; DRPLA, Dentatorubral-pallidoluysian atrophy; EEG, electroencephalogram; EMG, electromyography; FDG-PET, fluorodeoxyglucose-positron emission tomography; FOG, freezing of gait; FXTAS, Fragile X tremor-ataxia syndrome; FA, Friedreich’s ataxia; GAD, glutamate decarboxylase isotype; HIV, human immunodeficiency virus; HSP, hereditary spastic paraplegia; LDOPA, levodopa; LGI1, Leucine-rich-glioma-inactivated-1; LP, lumbar puncture; MCP, middle cerebellar peduncle; MIBG, metaiodobenzylguanidine; MSA-c, MSA with predominant cerebellar ataxia; MSA-p, MSA with predominant parkinsonism; MS, multiple sclerosis; MRI, magnetic resonance imaging; NGS, next-generation sequencing; OCB, oligoclonal bands; OH, orthostatic hypotension; PAF, primary autonomic failure; PD, Parkinson’s disease; PSP, progressive supranuclear palsy; PSP-P, PSP with predominant parkinsonism; QSART, Quantitative sudomotor axon reflex test; RBD, REM sleep behavior disorder; SCA, spinocerebellar ataxias; SPECT, single-photon emission computerized tomography; SPG7, spastic paraplegia 7; SPS, Stiff-person syndrome; WML, white matter lesions; y, years.

NEURONAL ANTIBODY-MEDIATED DISEASES

In recent years, many neuronal autoantibodies have been discovered, including antibodies targeting intracellular antigens and neuronal-surface antigens [12, 13]. Such diseases are not all tumor-associated, as most often occurs with intracellular antigen-targeting antibodies, but there are exceptions to this rule (e.g., GAD is an intracellular antigen and is very seldomly tumor-associated). Paraneoplastic neurological syndromes may be therapy-refractive and assume an unrelenting progressive course, however, other neuronal antibody-mediated diseases may present with a more subacute/chronic disease pattern, mimicking movement disorders of neurodegenerative or genetic etiologies, rendering their prompt diagnosis of utmost importance since these diseases are potentially amenable to treatment [12, 13]. Each autoantibody exhibits a relatively homogeneous phenotypic spectrum, with some movement disorders being very specific and reminiscent of a particu-
Table 2
Review of current diagnostic criteria for multiple system atrophy (MSA) [2]

| Mandatory requirements for clinical diagnosis of MSA | Symptom onset after 30 years of age  |
|------------------------------------------------------|--------------------------------------|
|                                                      | absence of family history            |
|                                                      | progressive disease course           |
| Neuropathologically established MSA                  | postmortem neuropathologic findings: |
|                                                      | CNS alpha-synuclein–positive glial  |
|                                                      | cytoplasmic inclusions with         |
|                                                      | neurodegenerative changes in         |
|                                                      | striatonigral or                    |
|                                                      | olivopontocerebellar structures     |
| Clinically established MSA                           |                                       |
| Clinically probable MSA                              |                                       |
| Core clinical features                               | dysautonomia *(at least one)*:       |
|                                                      | urinary urge, incontinence or        |
|                                                      | unexplained voiding difficulties or  |
|                                                      | orthostatic hypotension) and         |
|                                                      | poorly levodopa-responsive          |
|                                                      | parkinsonism or cerebellar          |
|                                                      | syndrome *(at least 2)*              |
| Supportive clinical (motor or non-motor) features    | At least two:                        |
|                                                      | rapid progression                    |
|                                                      | moderate to severe postural instability |
|                                                      | severe dysphagia and/or severe speech impairment |
|                                                      | all within three years of motor onset |
|                                                      | craniocervical dystonia induced or   |
|                                                      | exacerbated by LDOPA in              |
|                                                      | the absence of limb dyskinesia       |
|                                                      | jerky myoclonic postural or kinetic |
|                                                      | tremor                              |
|                                                      | pyramidal signs                     |
|                                                      | postural deformities                |
|                                                      | stridor, inspiratory sighs          |
|                                                      | cold discolored hands and feet,      |
|                                                      | erectile dysfunction                |
|                                                      | pathologic laughter or crying       |
| Brain MRI markers suggestive of MSA                  | At least one                        |
|                                                      | atrophy of:                         |
|                                                      | putamen (and signal decrease on      |
|                                                      | iron-sensitive sequences)           |
|                                                      | middle cerebellar peduncle (MCP),    |
|                                                      | pons, or                             |
|                                                      | cerebellum (*)                      |
|                                                      | ‘hot cross bun’ sign                 |
|                                                      | increased diffusivity of putamen and |
|                                                      | middle cerebellar peduncle (*)       |
| Non-supporting features (against MSA diagnosis)      | None                                 |
|                                                      | significant and persistent beneficial response to dopaminergic |
|                                                      | medications                         |
|                                                      | unexplained anosmia                 |
|                                                      | fluctuating cognition with           |
|                                                      | early visuoperceptual impairment     |
|                                                      | recurrent visual hallucinations (not |
|                                                      | drug-induced) and/or                |
|                                                      | dementia within 3 years of disease   |
|                                                      | onset                                |
|                                                      | downgaze supranuclear palsy or slowing of vertical saccades |
|                                                      | brain MRI findings suggestive of an alternative diagnosis |
|                                                      | documentation of an alternative      |

CNS, Central nervous system; LDOPA, levodopa; MRI, magnetic resonance imaging; * considered for MSA-P.

**Table 2**

| review of current diagnostic criteria for multiple system atrophy (MSA) [2] |
|---|
| **Mandatory requirements for clinical diagnosis of MSA** |
| Symptom onset after 30 years of age |
| absence of family history |
| progressive disease course |
| **Neuropathologically established MSA** |
| postmortem neuropathologic findings: |
| CNS alpha-synuclein–positive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures |
| **Clinically established MSA** |
| **Clinically probable MSA** |
| **Core clinical features** |
| dysautonomia *(at least one)*: |
| urinary urge, incontinence or unexplained voiding difficulties or orthostatic hypotension) and poorly levodopa-responsive parkinsonism or cerebellar syndrome *(at least 2)* |
| **Supportive clinical (motor or non-motor) features** |
| At least two: |
| rapid progression |
| moderate to severe postural instability |
| severe dysphagia and/or severe speech impairment |
| all within three years of motor onset |
| craniocervical dystonia induced or exacerbated by LDOPA in the absence of limb dyskinesia |
| jerky myoclonic postural or kinetic tremor |
| pyramidal signs |
| postural deformities |
| stridor, inspiratory sighs |
| cold discolored hands and feet, erectile dysfunction |
| pathologic laughter or crying |
| **Brain MRI markers suggestive of MSA** |
| At least one |
| atrophy of: |
| putamen (and signal decrease on iron-sensitive sequences) |
| middle cerebellar peduncle (MCP), pons, or cerebellum (*) |
| ‘hot cross bun’ sign |
| increased diffusivity of putamen and middle cerebellar peduncle (*) |
| **Non-supporting features (against MSA diagnosis)** |
| None |
| significant and persistent beneficial response to dopaminergic medications |
| unexplained anosmia |
| fluctuating cognition with early visuoperceptual impairment |
| recurrent visual hallucinations (not drug-induced) and/or dementia within 3 years of disease onset |
| downgaze supranuclear palsy or slowing of vertical saccades |
| brain MRI findings suggestive of an alternative diagnosis |
| documentation of an alternative condition |

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| **Clinically established MSA** |
| **Clinically probable MSA** |
| **Core clinical features** |
| dysautonomia *(at least one)*: |
| urinary urge, incontinence or unexplained voiding difficulties or orthostatic hypotension) and poorly levodopa-responsive parkinsonism or cerebellar syndrome *(at least 2)* |
| **Supportive clinical (motor or non-motor) features** |
| At least two: |
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| moderate to severe postural instability |
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| craniocervical dystonia induced or exacerbated by LDOPA in the absence of limb dyskinesia |
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| brain MRI findings suggestive of an alternative diagnosis |
| documentation of an alternative condition |
syndromes [12, 13, 15, 16], with manifestations comprising movement disorders (parkinsonism, ataxia, myoclonus), sleep dysfunction, and dysautonomia (see Table 1). It is highly important to notice accompanying symptoms, since neuronal antibody-associated diseases hardly ever manifest as isolated movement disorders. For instance, seizures and/or refractory epilepsy are acknowledged manifestations of various neuronal antibody-mediated diseases that present with complex phenotypes which may include clinical signs suggestive of an MSA diagnosis, as discussed above (e.g., coexisting dysautonomia, movement and/or sleep disorders) [12, 13]. In this way, epileptic presentations or treatment-resistant epilepsy in a patient with parkinsonism and/or cerebellar signs should be considered a red-flag against an MSA diagnosis and more in favor of an autoimmune process, triggering the search for neuronal antibody-mediated diseases. Therefore, associated clinical signs are often the much-needed clue to alert the clinician to consider an immune-mediated etiology [13].

A SHORT NOTE ON ANCILLARY EXAMS

Because of the absence of established diagnostic biomarkers, the use of brain MRI to improve MSA diagnostic accuracy has increased [17]. Brain MRI can reveal certain suggestive signs, including atrophy of the putamen, MCP, pons, or cerebellum; these have been included among the MRI markers defined in the current diagnostic criteria, which are mandatory for a clinically established MSA diagnosis [2, 17] (Table 2). Additionally, several studies have reported that putaminal hypointensity, slit-like hyperintense putaminal rim, MCP hyperintensities, and the hot cross bun sign on T2-weighted images can point to MSA [17]. The ‘hot cross bun’ sign has also been added as an MRI marker of MSA in the most recent criteria [2]. Objective measurements such as the MCP width, anteroposterior diameter of the pons, pons area, and the putamen/caudate volume ratio may also provide good discrimination of MSA from other conditions [17]; these measurements have to be done manually. Iron-sensitive MRIs (including susceptibility-weighted imaging sequences) have also been more widely used in clinical practice, not exclusively for MSA, but also for neurodegenerative parkinsonisms, which can similarly be useful when evaluating such patients.

New MRI techniques are being developed and innovative ways to diagnose and monitor disease progression are being explored [17]. Brain MRI may also be helpful when trying to rule out alternative diagnoses [17] presenting as MSA mimics, such as SCAs [18]. In a recent study, pontine and MCP changes were exclusively prominent in early stage MSA-c comparing to SCAs, nonetheless the discriminating value of MRI signs decreased over time. Hence, disease duration should be considered when interpreting pontine and MCP changes in brain MRIs [18]. There are also potential MRI mimics of MSA that can actually complicate matters if clinical diagnostic doubt is already present, exemplified by Fragile X- associated tremor/ataxia syndrome (FXTAS) [19]. MRI T2 white matter hyperintense lesions in the MCP (‘MCP sign’) is a major radiological feature of FXTAS and its best recognized neuroimaging characteristic, followed by T2 hyperintensity of the splenium of the corpus callosum, which was found to be as frequent as MCP hyperintensities [19–21] and which may be useful in identifying patients with an absent MCP sign. This MCP sign may also exist in MSA. The characteristic putaminal rim described in MSA has not been described in FXTAS; however, this sign is neither specific, nor sensitive [20]. Other radiological findings such as white matter lesions in cerebrum or moderate/severe generalized atrophy are also included as minor radiological features in FXTAS diagnostic criteria [19]. Considering the latter, its major clinical features are intention tremor and ataxia, with parkinsonism included as a minor clinical feature. Associated characteristics have been recognized, despite not being included in the mandatory criteria, which include myoclonus, executive dysfunction, dysautonomia, psychiatric comorbidities, sleep apnea, and neuropathy (length-dependent neuropathy, non-length dependent sensory neuropathy, small fiber painful neuropathy) [19]. Nevertheless, brain MRI is a useful tool in this particular differential diagnosis, since FXTAS will rarely present with the MCP sign as the only abnormal MRI finding [19, 20]. In this setting, the combined clinical and MRI findings should be weighted, and FMR1 gene testing is encouraged, particularly in men with an ataxic-predominant presentation and/or with suspicious MRI findings [19]. Another example is the presence of the ‘hot cross bun’ sign in other causes of pontocerebellar degeneration, such as SCAs [18].

Despite the inability of DaT-SPECT scans to distinguish between the various different neurode-
generative parkinsonian syndromes, it may be useful to differentiate MSA-c (with an abnormal scan) from other adult-onset cerebellar ataxias in patients who lack parkinsonian features (and where the scan will be normal) [5, 22]. Conversely, FDG-PET may be helpful in patients with predominantly parkinsonian features but no cerebellar ataxia [5, 22]. Specific hypometabolic patterns have been depicted in MSA patients, with the most distinctive finding in MSA-p being a reduction in $^{18}$FDG-PET uptake in the putamen bilaterally, with a rostro-caudal gradient [22]. Such a finding is both sensitive ($\approx 95\%$) and specific ($\approx 100\%$) for distinguishing PD from MSA-p [23]. Decreased $^{18}$FDG-PET uptake can similarly be noticed in the thalamus, brainstem and cortical areas [22], which paved the way for the inclusion of hypometabolism of the (posterior) putamen, mesencephalic region and cerebellum as being supportive for MSA-p in the 2008 MSA consensus diagnostic criteria [5]. Currently, FDG-PET markers are also supportive biomarkers for MSA diagnosis [2]. In MSA-c patients, hypometabolism of the anterior cerebellar hemispheres and the vermis can be detected one year after motor-symptom onset, even though hypometabolism of the putamen can also be observed [22, 24], constituting a supportive biomarker for MSA-c diagnosis [2, 5, 22]. Still, there is a clear variability in the adoption of nuclear imaging modalities within the diagnostic process of MSA. Reasons for this include the high costs, greater difficulty accessing these complementary exams, questions regarding their utility at an individual level (since results have mostly been generated by group comparisons), lack of necessary expertise for adequate interpretation in some clinics, and the fact that imaging findings per se will never allow attainment of a diagnostic certainty level of clinically established MSA.

Genetic testing takes on particular importance when considering the MSA-c phenotype (Table 1), which has been increasingly discussed and recommended in the last ten years [25]. We propose that a SCA panel (1-2-3-6-7-17), and DRPLA, FXTAS (men), SPG7 and RFC1 testing could constitute a comprehensive battery to exclude the main genetic MSA-c mimics, in all cases with an MSA-c-like phenotype. Considering MSA-p, creation of a specific testing panel is more difficult. Nevertheless, genetic testing for patients with parkinsonism without cerebellar symptoms who meet the diagnostic criteria for MSA (based on clinical grounds) has been suggested, including SCA types 2, 3, and 17 [25]. We suggest that broader genetic testing could be considered if red-flags against MSA are present.

In summary, although the diagnosis of MSA during life remains mostly a clinical one, there are various ancillary tests available, ranging from advanced structural MRI and nuclear imaging, to genetic testing and blood/CSF screens for autoantibodies, that can add levels of certainty to an MSA diagnosis, and that can be of assistance in ruling out or establishing alternative diagnoses.

CONCLUDING REMARKS

MSA is usually a relatively rapidly progressive disease, for which there is still no modifying therapy available [3]. An accurate diagnosis is vital, since a misdiagnosis may lead to withholding treatment in a treatable disorder or provision of a wrong prognosis [3]. PD and other atypical parkinsonisms, such as DLB and PSP, are usually considered to be the main culprits of an MSA misdiagnosis, but many other diseases can mimic MSA [3, 4]. Brain MRI is a key element when evaluating parkinsonian and cerebellar syndromes [22]. This allows clinicians to verify characteristic MSA neuroimaging patterns or potentially discover informative clues towards certain mimics. Although ancillary tests can contribute to the diagnosis of MSA and should be performed when possible, the diagnosis of clinically established or clinically probable MSA still remains much dependent on clinical history and the neurological examination [22]. Notwithstanding available consensus criteria for clinical diagnosis and advances in diagnostic techniques, MSA diagnostic accuracy remains sub-optimal [4, 6, 22]. Neurologists should be familiar with some MSA mimics in order to establish a correct diagnosis in a shorter period of time [3].

CONFLICT OF INTEREST

Bart van de Warrenburg receives research support from ZonMw, Hersenstichting, Gossweiler Foundation, Radboud University Medical Center, and uniQure; receives royalties from BSL – Springer Nature, and has served on a scientific advisory board of uniQure and Servier.

Bastiaan Bloem serves as the co-Editor in Chief for the Journal of Parkinson’s Disease, serves on the editorial boards of Practical Neurology and Digital Biomarkers, has received fees from serving on the scientific advisory board for UCB, Kyowa Kirin,
Zambon and the Critical Path Institute (paid to the Institute), has received fees for speaking at conferences from AbbVie, Biogen, UCB, Zambon, Roche, GE Healthcare, Oruen, Novartis and Bial (paid to the Institute), and has received research support from the Netherlands Organization for Health Research and Development, the Michael J Fox Foundation, UCB, the Stichting Parkinson Fonds, Hersenstichting Nederland, de Stichting Woelse Waard, Stichting Alkemade-Keuls, de Maag Lever Darm Stichting Nederland, de Stichting Woelse Waard, Stichting UCB, the Stichting Parkinson Fonds, Hersenstichting Nederland, the Michael J Fox Foundation, the Netherlands Organization for Health Research and Development, the Michael J Fox Foundation, the Netherlands Organization for Health Research and Development, and has received research support from GE Healthcare, Oruen, Novartis and Bial (paid to the Institute). The other authors have no conflict of interest to report.

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