Journal of Parkinson's Disease 12 (2022) 2015–2027
DOI 10.3233/JPD-223392
IOS Press

Review

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

Linda Azevedo Kauppila[a,b], Susanne E.M. Ten Holter[b], Bart van de Warrenburg[b] and Bastiaan R. Bloem[b,*]
[a]*CNS – Campus Neurológico, Lisbon, Portugal*
[b]*Department of Neurology, Center of Expertise for Parkinson & Movement Disorders, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands*

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 [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

*Correspondence to: Prof. Bastiaan R. Bloem, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3615202; E-mail: bas.bloem@radboudumc.nl.

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 videoclips 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 α-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.

Table 1
MSA differential diagnosis

Etiology	Differential diagnosis	Mimic of MSAc/ MSAp/Both	Important clinical information (Overlapping features between differentials and red flags against MSA)	Complementary diagnostic methods
Genetic	SCAs 1, 3, 7, 17 2, 6 12 [3, 8]	Both MSA-c MSA-p	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 *Red flags: family history, cognitive impairment, peripheral neuropathy, seizures, visual loss (retinal disease)*	Genetic testing
	DRPLA [8, 9, 26]	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
	FXTAS [20]	Both, mostly MSA-c	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 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)* [29–34]	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 neuronopathy, prolonged disease course (CANVAS); absence of RBD, brainstem atrophy on brain MRI (suggestive of MSAc)*	Genetic testing for *RFC1* EMG Video-oculography, videonystagmography
	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, aminoacids, 5-methyltetrahydrofolate)* *Cardiac evaluation* *EEG, neuroimaging*

(*Continued*)

Table 1
(*Continued*)

Etiology	Differential diagnosis	Mimic of MSAc/ MSAp/Both	Important clinical information (Overlapping features between differentials and red flags against MSA)	Complementary diagnostic methods
Neuro-degenerative	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 visuospatial 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*)

Table 1
(*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 epilepsia partialis continua) [limbic encephalitis], opsoclonus-myoclonus syndrome, retinopathy, sensorineuronal hearing loss, sensitive neuronopathy, 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, encephalopathy; 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	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	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	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)*	

(*Continued*)

Table 1
(*Continued*)

Etiology	Differential diagnosis	Mimic of MSAc/ MSAp/Both	Important clinical information (Overlapping features between differentials and red flags against MSA)	Complementary diagnostic methods
	Anti-GAD ataxia [13, 15, 16]	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 AO (±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 AO; cerebellar symptoms are very prevalent in these patients *Red flags: mean AO ± 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 [48–50]	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, gaze-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; DLB, 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 unremittingly 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	autonomic dysfunction parkinsonism **or** cerebellar syndrome *(at least 2)*
supportive clinical (motor or non-motor) features	At least two	At least one
	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	None
	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)	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	

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

lar autoantibody. Some syndromes, despite being less specific, should raise suspicion of a neuronal autoimmune disease [13]. These include cases of autoimmune cerebellar ataxia, with a diverse clinical presentation and a known association with numerous neuronal autoantibodies, but its combination with further clinical signs and symptoms, e.g., dysautonomia, insomnia or seizures, may evoke a greater likelihood of an autoimmune etiology, especially if a subacute onset and rapidly progressive cerebellar syndrome are identified [13].

Important neuronal antibodies to consider within the range of MSA mimics include anti-LGI1, CASPR2, IgLON5, GAD, and DPPX associated

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 (≈95%) and specific (≈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, Parkinson NL, Davis Phinney Foundation, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, Nothing Impossible and the Parkinson Vereniging, outside the submitted work.

The other authors have no conflict of interest to report.

REFERENCES

[1] Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. *Lancet* **397**, 2284-2303.

[2] Wenning GK, Stankovic I, Vignatelli L, Fanciulli A, Calandra-Buonaura G, Seppi K, Palma JA, Meissner WG, Krismer F, Berg D, Cortelli P, Freeman R, Halliday G, Höglinger G, Lang A, Ling H, Litvan I, Low P, Miki Y, Panicker J, Pellecchia MT, Quinn N, Sakakibara R, Stamelou M, Tolosa E, Tsuji S, Warner T, Poewe W, Kaufmann H (2022) The Movement Disorder Society criteria for the diagnosis of multiple system atrophy. *Mov Disord* **37**, 1131-1148.

[3] Kim HJ, Stamelou M, Jeon B (2016) Multiple system atrophy-mimicking conditions: Diagnostic challenges. *Parkinsonism Relat Disord* **22**(Suppl 1), S12-S15.

[4] Koga S, Aoki N, Uitti RJ, van Gerpen JA, Cheshire WP, Josephs KA, Wszolek ZK, Langston JW, Dickson DW (2015) When DLB, PD, and PSP masquerade as MSA: An autopsy study of 134 patients. *Neurology* **85**, 404-412.

[5] Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M (2008) Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* **71**, 670-676.

[6] Miki Y, Foti SC, Asi YT, Tsushima E, Quinn N, Ling H, Holton JL (2019) Improving diagnostic accuracy of multiple system atrophy: A clinicopathological study. *Brain* **142**, 2813-2827.

[7] Thongchuam Y, Panyakaew P, Bhidayasiri R (2020) Orofacial dystonia and associated bulbar symptoms in multiple system atrophy: A blinded video analysis. *J Neurol Sci* **417**, 116992.

[8] Soong BW, Morrison PJ (2018) Spinocerebellar ataxias. *Handb Clin Neurol* **155**, 143-174.

[9] Carroll LS, Massey TH, Wardle M, Peall KJ (2018) Dentatorubral-pallidoluysian atrophy: An update. *Tremor Other Hyperkinet Mov (N Y)* **8**, 577.

[10] Lieto M, Roca A, Santorelli FM, Fico T, De Michele G, Bellofatto M, Saccà F, De Michele G, Filla A (2019) Degenerative and acquired sporadic adult onset ataxia. *Neurol Sci* **40**, 1335-1342.

[11] Ricigliano VAG, Fossati B, Saraceno L, Cavalli M, Bazzigaluppi E, Meola G (2018) MSA mimic? Rare occurrence of anti-hu autonomic failure and thymoma in a patient with parkinsonism: Case report and literature review. *Front Neurosci* **12**, 17.

[12] Leypoldt F, Wandinger KP (2014) Paraneoplastic neurological syndromes. *Clin Exp Immunol* **175**, 336-348.

[13] Gövert F, Leypoldt F, Junker R, Wandinger KP, Deuschl G, Bhatia KP, Balint B (2020) Antibody-related movement disorders - a comprehensive review of phenotype-autoantibody correlations and a guide to testing. *Neurol Res Pract* **2**, 6.

[14] Schlapakow E, Keil VC, Paus M, Kornblum C, Hattingen E, Klockgether T (2020) Multiple system atrophy mimicry in MRI: Watch out for paraneoplastic rhombencephalitis. *J Clin Neurosci* **76**, 238-240.

[15] Ariño H, Gresa-Arribas N, Blanco Y, Martínez-Hernández E, Sabater L, Petit-Pedrol M, Rouco I, Bataller L, Dalmau JO, Saiz A, Graus F (2014) Cerebellar ataxia and glutamic acid decarboxylase antibodies: Immunologic profile and long-term effect of immunotherapy. *JAMA Neurol* **71**, 1009-1016.

[16] Manto M, Mitoma H, Hampe CS (2019) Anti-GAD antibodies and the cerebellum: Where do we stand? *Cerebellum* **18**, 153-156.

[17] Kim HJ, Jeon B, Fung VSC (2016) Role of magnetic resonance imaging in the diagnosis of multiple system atrophy. *Mov Disord Clin Pract* **4**, 12-20.

[18] Kim M, Ahn JH, Cho Y, Kim JS, Youn J, Cho JW (2019). Differential value of brain magnetic resonance imaging in multiple system atrophy cerebellar phenotype and spinocerebellar ataxias. *Sci Rep* **9**, 17329.

[19] Hall DA, Birch RC, Anheim M, Jønch AE, Pintado E, O'Keefe J, Trollor JN, Stebbins GT, Hagerman RJ, Fahn S, Berry-Kravis E, Leehey MA (2014) Emerging topics in FXTAS. *J Neurodev Disord* **6**, 31.

[20] Stamelou M, Quinn NP, Bhatia KP (2013) "Atypical" atypical parkinsonism: New genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy—a diagnostic guide. *Mov Disord* **28**, 1184-1199.

[21] Apartis E, Blancher A, Meissner WG, Guyant-Maréchal L, Maltête D, De Broucker T, Legrand AP, Bouzenada H, Thanh HT, Sallansonnet-Froment M, Wang A, Tison F, Roué-Jagot C, Sedel F, Charles P, Whalen S, Héron D, Thobois S, Poisson A, Lesca G, Ouvrard-Hernandez AM, Fraix V, Palfi S, Habert MO, Gaymard B, Dussaule JC, Pollak P, Vidailhet M, Durr A, Barbot JC, Gourlet V, Brice A, Anheim M (2012) FXTAS: New insights and the need for revised diagnostic criteria. *Neurology* **79**, 1898-907.

[22] Palma JA, Norcliffe-Kaufmann L, Kaufmann H (2018) Diagnosis of multiple system atrophy. *Auton Neurosci* **211**, 15-25.

[23] Brooks DJ, Seppi K (2009) Neuroimaging Working Group on MSA. Proposed neuroimaging criteria for the diagnosis of multiple system atrophy. *Mov Disord* **24**, 949-964.

[24] Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS, Eidelberg D (2005) FDG PET in the differential diagnosis of parkinsonian disorders. *Neuroimage* **26**, 912-921.

[25] Kim HJ, Jeon BS, Shin J, Lee WW, Park H, Jung YJ, Ehm G (2014) Should genetic testing for SCAs be included in the diagnostic workup for MSA? *Neurology* **83**, 1733-1738.

[26] Vale J, Bugalho P, Silveira I, Sequeiros J, Guimarães J, Coutinho P (2010) Autosomal dominant cerebellar ataxia:

Frequency analysis and clinical characterization of 45 families from Portugal. *Eur J Neurol* **17**, 124-128.

[27] Shribman S, Reid E, Crosby AH, Houlden H, Warner TT (2019) Hereditary spastic paraplegia: From diagnosis to emerging therapeutic approaches. *Lancet Neurol* **18**, 1136-1146.

[28] Hewamadduma CA, Hoggard N, O'Malley R, Robinson MK, Beauchamp NJ, Segamogaite R, Martindale J, Rodgers T, Rao G, Sarrigiannis P, Shanmugarajah P, Zis P, Sharrack B, McDermott CJ, Shaw PJ, Hadjivassiliou M (2018) Novel genotype-phenotype and MRI correlations in a large cohort of patients with SPG7 mutations. *Neurol Genet* **4**, e279.

[29] Wu TY, Taylor JM, Kilfoyle DH, Smith AD, McGuinness BJ, Simpson MP, Walker EB, Bergin PS, Cleland JC, Hutchinson DO, Anderson NE, Snow BJ, Anderson TJ, Paermentier LA, Cutfield NJ, Chancellor AM, Mossman SS, Roxburgh RH (2014) Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome. *Brain* **137**, 2649-2656.

[30] Szmulewicz DJ, Roberts L, McLean CA, MacDougall HG, Halmagyi GM, Storey E (2016) Proposed diagnostic criteria for cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). *Neurol Clin Pract* **6**, 61-68.

[31] Aboud Syriani D, Wong D, Andani S, De Gusmao CM, Mao Y, Sanyoura M, Glotzer G, Lockhart PJ, Hassin-Baer S, Khurana V, Gomez CM, Perlman S, Das S, Fogel BL (2020) Prevalence of *RFC1*-mediated spinocerebellar ataxia in a North American ataxia cohort. *Neurol Genet* **6**, e440.

[32] Cortese A, Tozza S, Yau WY, Rossi S, Beecroft SJ, Jaunmuktane Z, Dyer Z, Ravenscroft G, Lamont PJ, Mossman S, Chancellor A, Maisonobe T, Pereon Y, Cauquil C, Colnaghi S, Mallucci G, Curro R, Tomaselli PJ, Thomas-Black G, Sullivan R, Efthymiou S, Rossor AM, Laurá M, Pipis M, Horga A, Polke J, Kaski D, Horvath R, Chinnery PF, Marques W, Tassorelli C, Devigili G, Leonardis L, Wood NW, Bronstein A, Giunti P, Züchner S, Stojkovic T, Laing N, Roxburgh RH, Houlden H, Reilly MM (2020) Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. *Brain* **143**, 480-490.

[33] Dominik N, Galassi Deforie V, Cortese A, Houlden H (2021) CANVAS: A late onset ataxia due to biallelic intronic AAGGG expansions. *J Neurol* **268**, 1119-1126.

[34] Sullivan R, Yau WY, Chelban V, Rossi S, Dominik N, O'Connor E, Hardy J, Wood N, Cortese A, Houlden H (2021) *RFC1*-related ataxia is a mimic of early multiple system atrophy. *J Neurol Neurosurg Psychiatry* **92**, 444-446.

[35] Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, Anselm I, Cohen BH, Falk MJ, Greene C, Gropman AL, Haas R, Hirano M, Morgan P, Sims K, Tarnopolsky M, Van Hove JL, Wolfe L, DiMauro S (2015) Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genet Med* **17**, 689-701.

[36] Cohen BH (2013) Neuromuscular and systemic presentations in adults: Diagnoses beyond MERRF and MELAS. *Neurotherapeutics* **10**, 227-242.

[37] Zeviani M, Simonati A, Bindoff LA (2012) Ataxia in mitochondrial disorders. *Handb Clin Neurol* **103**, 359-372.

[38] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* **30**, 1591-1601.

[39] Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell JL, Arzberger T, Englund E, Gelpi E, Giese A, Irwin DJ, Meissner WG, Pantelyat A, Rajput A, van Swieten JC, Troakes C, Antonini A, Bhatia KP, Bordelon Y, Compta Y, Corvol JC, Colosimo C, Dickson DW, Dodel R, Ferguson L, Grossman M, Kassubek J, Krismer F, Levin J, Lorenzl S, Morris HR, Nestor P, Oertel WH, Poewe W, Rabinovici G, Rowe JB, Schellenberg GD, Seppi K, van Eimeren T, Wenning GK, Boxer AL, Golbe LI, Litvan I, Movement Disorder Society-endorsed PSP Study Group (2017) Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society criteria. *Mov Disord* **32**, 853-864.

[40] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **89**, 88-100.

[41] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Tröster AI, Vidailhet M, Weiner WJ (2013) Criteria for the diagnosis of corticobasal degeneration. *Neurology* **80**, 496-503.

[42] Abele M, Bürk K, Schöls L, Schwartz S, Besenthal I, Dichgans J, Zühlke C, Riess O, Klockgether T (2002) The aetiology of sporadic adult-onset ataxia. *Brain* **125**, 961-968.

[43] Klockgether T (2018) Sporadic adult-onset ataxia. *Handb Clin Neurol* **155**, 217-225.

[44] Coon EA, Singer W, Low PA (2019) Pure autonomic failure. *Mayo Clin Proc* **94**, 2087-2098.

[45] Mearns ES, Taylor A, Thomas Craig KJ, Puglielli S, Leffler DA, Sanders DS, Lebwohl B, Hadjivassiliou M (2019) Neurological manifestations of neuropathy and ataxia in celiac disease: A systematic review. *Nutrients* **11**, 380.

[46] Wilkins A (2017) Cerebellar dysfunction in multiple sclerosis. *Front Neurol* **8**, 312.

[47] Pedroso JL, Vale TC, Gama MTD, Ribas G, Kristochik JCG, Germiniani FMB, Fink MCDDS, Oliveira ACP, Teive HAG, Barsottini OG (2018) Cerebellar degeneration and progressive ataxia associated with HIV-virus infection. *Parkinsonism Relat Disord* **54**, 95-98.

[48] Mostile G, Nicoletti A, Zappia M (2018) Vascular parkinsonism: Still looking for a diagnosis. *Front Neurol* **9**, 411.

[49] Korczyn AD (2015) Vascular parkinsonism–characteristics, pathogenesis and treatment. *Nat Rev Neurol* **11**, 319-326.

[50] Koga S, Roemer SF, Tipton PW, Low PA, Josephs KA, Dickson DW (2020) Cerebrovascular pathology and misdiagnosis of multiple system atrophy: An autopsy study. *Parkinsonism Relat Disord* **75**, 34-40.

[51] Williams MA, Relkin NR (2013) Diagnosis and management of idiopathic normal-pressure hydrocephalus. *Neurol Clin Pract* **3**, 375-385.

[52] Maltête D, Guyant-Maréchal L, Mihout B, Hannequin D (2006) Movement disorders and Creutzfeldt-Jakob disease: A review. *Parkinsonism Relat Disord* **12**, 65-71.

[53] Rodriguez-Porcel F, Ciarlariello VB, Dwivedi AK, Lovera L, Da Prat G, Lopez-Castellanos R, Suri R, Laub H, Walker RH, Barsottini O, Pedroso JL, Espay AJ (2019) Movement disorders in prionopathies: A systematic review. *Tremor Other Hyperkinet Mov (N Y)* **12**, 9.