Multiple system atrophy

in

Parkinsonism beyond Parkinson's disease

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Abstract

Multiple system atrophy (MSA) is a sporadic, adult-onset, relentlessly progressive neurodegenerative disorder, clinically characterized by various combinations of autonomic failure, parkinsonism and ataxia. The neuropathological hallmark of MSA are glial cytoplasmic inclusions consisting of misfolded α-synuclein. Selective atrophy and neuronal loss in striatonigral and olivopontocerebellar systems underlie the division into two main motor phenotypes of MSA-parkinsonian type and MSA-cerebellar type. Isolated autonomic failure and REM sleep behavior disorder are common premotor features of MSA. Beyond the core clinical symptoms, MSA manifests with a number of non-motor and motor features. Red flags highly specific for MSA may provide clues for a correct diagnosis. Diagnostic accuracy of the second consensus criteria is suboptimal particularly in early disease stages. In this chapter, the authors discuss the historical milestones, etiopathogenesis, neuropathological findings, clinical features, red flags, differential diagnosis, diagnostic criteria, imaging and other biomarkers, current treatment, unmet needs and future treatments for MSA.

I. The history of multiple system atrophy

The milestones

The historical roots of multiple system atrophy (MSA) date back to the early 20th century, when J. Dejerine and A. Thomas, neurologists at the Salpêtrière hospitals in Paris, first described two patients with adult-onset sporadic ataxia, who eventually developed extra-pyramidal, urinary and probably postural hypotensive symptoms, dying few years afterwards. Neuropathological examination of one of these cases showed severe olivopontocerebellar atrophy (Figure 1)[1].

Later, in 1925, S. Bradbury and C. Egglestone from the Cornell University in New York described three cases of postural hypotension accompanied by anhidrosis and impotence. For the first time, these authors postulated the existence of neurogenic orthostatic hypotension (OH) and paved the way to the identification of primary disorders of the autonomic nervous system, to which MSA belongs[2].

Decades later, in 1960, G.M. Shy and G.A. Drager from the US National Institute of Health described a clinical syndrome characterized by marked multi-domain autonomic failure associated with severe parkinsonism and ataxia[3]. One year later, in 1961, R.D. Adams reported patients with Shy Drager syndrome to have striatonigral degeneration with additional cerebellar, olivary and pontine involvement at neuropathological examination[4].

Reflecting the multifaceted clinical presentation of MSA, scientists had not yet understood by that time that they had approached the disease like *"blindfolded men examining different parts of an elephant and coming away with different impressions of the nature of the beast"*[1].

First in 1969 the British J.G. Graham and D.R. Oppenheimer identified the common denominator underlying the syndromes described by Dejerine and Thomas, Bradbury and Egglestone and Shy and Drager. "*Wishing to avoid the multiplication of names for disease entities, which in fact are merely the expressions of neuronal atrophy in a variety of overlapping combinations…"* they coined the umbrella term multiple system atrophy[5].

The neuropathological hallmark of MSA are glial cytoplasmic inclusions, which were first described in 1989 by M.I. Papp and colleagues[6]. Ten years later, M.G. Spillantini and coworkers identified α-synuclein to be the main constituent of such glial cytoplasmic inclusion, providing a pathological link between Parkinson's disease (PD), dementia with Lewy bodies (DLB) and MSA: all α-synucleinopathies, in fact[7].

In recent years, major insights have been achieved into MSA natural history and its premotor stages[8, 9], which include isolated autonomic failure or REM sleep behavior disorders (RBD) predating by years the full blown clinical presentation of MSA[10-13]. Such detailed knowledge of MSA disease course is being exploited for an optimized design of upcoming neuroprotective trials.

Diagnostic criteria

Until 1989, the only available diagnostic criteria for MSA were those from the Mayo Clinic, which defined a diagnosis of MSA in the presence of autonomic failure plus parkinsonism or cerebellar ataxia. Without considering L-Dopa responsiveness, such criteria did not differentiate MSA from PD with autonomic failure. To cover this gap, in 1989, N. Quinn from the National Queen Square Hospital in London proposed a 1st set of criteria, in which he distinguished three degrees of diagnostic certainty (possible, probable and definite MSA),

with supporting warning signs (the so called “red flags”) and exclusion criteria[1]. Building upon this approach, the 1st consensus conference on the definition of MSA diagnostic criteria took place 10 years later in Minneapolis with the sponsorship of the American Autonomic Society and of the American Academy of Neurology[14]. The 2nd consensus statement on MSA diagnosis was published in 2008 with the sponsorship of the National Institute of Health and of the American Academy of Neurology and provided a simplified description of clinical features required for the clinical diagnosis of MSA[15].

Striving for a cure

Following the identification of the pivotal role of α-synuclein glial cytoplasmic inclusions in the development of MSA, both cellular and transgenic animal models of MSA have been developed in the last decades[16-18]. Latter provided preclinical experimental evidence for several interventional trials, which have been run by research consortia such as the European Multiple System Atrophy Study Group, the French Multiple System Atrophy Reference Center, the U.S. Autonomic Disorders Consortium and other dedicated research teams worldwide.

Despite preclinical evidence of neuroprotection, recombinant human growth hormone[19], minocycline[20], riluzole[21], rifampicin[22], rasagiline[23] and epigallocatechin-gallate[24] showed no benefit.

A randomized, placebo-controlled trial of combined intra-arterial and intravenous autologous mesenchymal stem cells attenuated clinical progression in patients with MSA of cerebellar type[25]. In another recent open-label trial, intrathecal administration of autologous mesenchymal stem cells was also shown to be associated with dose-dependent clues of efficacy in patients with early MSA[26].

Other newly concluded and currently ongoing studies adopted immunomodulatory approaches, such as active α-synuclein immunization or myeloperoxidase inhibition and will hopefully provide evidence of neuroprotection in the next future.

MSA advocacies

The first advocacy groups helping families affected by MSA were grounded in the United States in the 80s. Spouses of MSA patients, together with neurologist David Robertson from the Vanderbilt University in Nashville, founded the non-profit Shy-Drager Multiple System Atrophy Support Group, in 2013 renamed as the MSA-Coalition (www.multiplesystematrophy.org)[27]. The MSA-Coalition provides a toll-free helpline for affected families, organizes dedicated support conferences and, thanks to very effective fundraising campaigns, finances several strategic research projects, like the Global MSA Registry, an online platform bringing together the clinical experience of several MSA research teams world-wide[28].

In the UK, patient advocate Sarah Matheson founded a dedicated MSA charity after being diagnosed with MSA on her own. Initially called Sarah Matheson Trust, it was later renamed as the Multiple System Atrophy (MSA) Trust (www.msatrust.org.uk) and also focuses on alleviating the feeling of isolation of MSA patients and their families, as well financing promising research protocols.

In 2010 the "Miracles for MSA" Facebook page created by Anna Langerveld advocated for March to be declared the Multiple System Atrophy Awareness Month. In the same year, advocates led by Ritje Schouppe-Moons in Belgium declared October 3rd as World Multiple

System Atrophy Day: on this day candles are lit at 8 pm in each local time zone, symbolizing awareness and unity for the cause of MSA.

II. Definition and neuropathology

MSA is defined as a sporadic adult-onset relentlessly progressive and fatal neurodegenerative disorder clinically characterized by various combinations of autonomic failure, parkinsonism and ataxia[29]. The presence of oligodendroglial cytoplasmatic inclusions consisting of misfolded α-synuclein is required for a definite diagnosis of MSA on postmortem examination[15]. Characteristic lesions include selective atrophy and neuronal loss in striatonigral and olivopontocerebellar systems[30]. Neurodegenerative changes also affect other parts of the central, autonomic and peripheral nervous systems[30]. Different combinations of motor and non-motor deficits in MSA result from a variable regional distribution and severity of underlying neuropathology[29].

Two main morphological variants of striatonigral degeneration (SND) and olivopontocerebellar atrophy (OPCA) strongly correlate with two major motor phenotypes of MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar features (MSA-C) respectively[31]. Macroscopically, SND is characterized by atrophy and dark discoloration due to lipofuscin, neuromelanin and iron accumulation in dorsolateral putamen and caudatus and pallor of substantia nigra and locus coeruleus. In OPCA, there is a severe atrophy of cerebellar folia, pontine basis and middle cerebellar peduncle, dark discoloration of cerebellar white matter and blurring of inferior olivary nucleus with spared superior cerebellar peduncles[32].

Atrophy, neuronal loss, pathologic inclusions and reactive astrogliosis are observed microscopically. In addition to abundant glial cytoplasmic inclusions, there are less frequent α-synuclein immunoreactive nuclear inclusions both in oligodendroglia and neurons and neuronal cytoplasmic inclusions[32].

Glial cytoplasmic inclusions are composed of filamentous α-synuclein and other proteins including ubiquitin, tau, LRRK2, DJ-1, p25α, GFAP, MBP, among others[32]. Load of glial cytoplasmic inclusions increases with disease progression[31]. Primary motor and premotor cortices are the sites of most abundant accumulation of glial cytoplasmic inclusions. There is an inverse correlation between the burden of glial cytoplasmic inclusions and the degree of neurodegeneration[33]. The highest number of glial cytoplasmic inclusions could be found in mildly to moderately affected white matter and lowest number in severely affected grey matter[33].

The main sites of degeneration in MSA-P are the dorsolateral putamen and caudate nucleus, whereas the substantia nigra pars compacta, globus pallidus and subthalamic nucleus are affected to a lesser extent. In MSA-C, the Purkinje cells, vermis, dentate nucleus, pontine basis and the inferior olivary nucleus are primarily degenerated, and basal ganglia are only mildly affected[32]. The proposed grading system based on predominant affection of SND or OPCA (each scored 0-3; SND3 + OPCA1 for MSA-P, OPCA3 + SND1 for MSA-C) demonstrated that mixed morphological presentations are present in a majority of MSA cases[34, 35]. “Minimal-change” MSA is characterized by a localized neuronal loss in substantia nigra and locus coeruleus and widespread glial cytoplasmic inclusions. This peculiar variant is associated with an earlier disease onset, early OH and major respiratory impairment[36, 37].

Disruption of the central autonomic network results in autonomic failure in MSA[38, 39]. The dorsal vagal nucleus, sacral part of intermediolateral column of the spinal cord and Onuf's nucleus are universally affected in MSA-P and MSA-C and contribute to erectile and urinary dysfunction[40]. Affection of the hypothalamus, locus coeruleus, pontine micturition center, substantia nigra and Purkinje cells also underpin urogenital symptoms[40]. OH arises from the degeneration of medullary cardiovascular centers, thoracic part of intermediolateral column of the spinal cord, sympathetic ganglia and to a lesser extent postganglionic fibers[40]. Degeneration of postganglionic sympathetic fibres reflects peripheral autonomic involvement, which occurs less frequently compared to PD and can be visualized in vivo employing the ^{123}I-MIBG cardiac scintigraphy or sudomotor function tests[41, 42].

Cortical and limbic glial cytoplasmic inclusions, Lewy-body like inclusions and frontal striatal deafferentation underlie cognitive impairment in MSA, whereas amyloid pathology is rare[43-45]. REM sleep behavior disorders develop after a neurodegeneration of the pedunculopontine nucleus and locus caeruleus projections[46]. Neurodegeneration of nucleus ambiguous, serotonergic nuclei raphe and cholinergic projections from pedunculopontine nucleus and laterodorsal tegmental nuclei leads to stridor and obstructive sleep apnea[40]. Affection of the medullary respiratory centers underpins the central hypoventilation in MSA[46]. Despite findings of glial cytoplasmic inclusions, neuronal loss and atrophy of the olfactory bulb are less pronounced compared to PD and account for preserved olfaction in patients with MSA[47]. Aggregates of α-synuclein are expressed in the cytoplasm of Schwann cells, but the relevance of this finding for clinically manifested peripheral neuropathy has not been elucidated yet[48].

Co-pathology of Lewy bodies found in 11% of European MSA cases was not replicated in a separate Japanese cohort[31, 49]. Several cases with dual pathology of MSA and progressive supranuclear palsy (PSP) have been reported[50].

III. Etiology and Pathophysiology

Etiology

No environmental factors have been associated with an increased risk of MSA. Like in PD, nicotine as well as alcohol consumption are less common in MSA than in healthy controls, possibly representing a pathophysiological link among α-synucleinopathies. An association with agricultural employment and occupational exposure to organic solvents, plastic monomers, pesticides and metal dusts has been reported in 2 case-control studies[51, 52], but not replicated in others[53].

MSA is generally considered a sporadic disease[29]. Nevertheless, MSA pedigrees with both autosomal dominant and autosomal recessive inheritance pattern have been reported in Europe and Asia[54-56].

A loss-of-function mutation in the COQ2 gene, coding for the coenzyme Q_{10} synthesizing enzyme, was reported in Japanese familial and sporadic MSA cases and is to date the only identified cause of monogenic MSA[57]. Coenzyme Q_{10} contributes to the electron transfer between complexes I, II and III of the mitochondrial respiratory chain and its loss-of-function suggests that mitochondrial dysfunction may play an important role in the pathogenesis of the disease[57, 58]. No COQ2 mutation was however detected in North American and European

MSA natives[59]. Similarly, a discordant loss of copy numbers of the SHC2 gene was observed in monozygotic twins and sporadic Japanese MSA patients, but in not American patients[60, 61].

Mutations, duplications and triplications of the SNCA gene, coding for α-synuclein, may cause familial PD with MSA traits in some members[62]. In particular, the G51D SNCA mutation reported in a British pedigree with autosomal dominant juvenile Parkinsonism showed neuropathological findings compatible with both PD and MSA[63]. Two single-nucleotide-polymorphisms of the SNCA locus showed a significant association with MSA in a large European series[64]. This association was confirmed in following replication studies[65], but not in the subsequent MSA genome-wide association study[59]. This same study, to date the largest run in European and North-American MSA patients, further identified single-nucleotide polymorphisms in the genes FBXO47, ELOVL7, EDN1, and MAPT, which may possibly contribute to the pathogenesis of MSA.

Gain of function mutations of the LRRK2 gene coding for the Serin/Threoninkinase 2 are responsible for 1% of sporadic and 4% of familial PD cases. Recently, two cases of pathologically proven MSA harboring LRRK2 mutations have been reported[66, 67], suggesting that α-synuclein hyperphosphorylation may represent another important mechanism of disease both in PD and MSA.

Beyond abovementioned MSA-related genetic mutations, an increasing number of other genetic conditions is being recognized to cause MSA-mimicries, the most frequent of these being SCA 17 mutations[68]. MSA mimicries should be always considered in case of an atypical disease course or additional features not typically belonging to the MSA core-spectrum[69].

Pathophysiology

The mechanisms underlying MSA pathogenesis remain to date not fully understood. Converging evidence from preclinical and postmortem studies suggests that both neuronal and glial dysfunction contribute to the development of the disease, which has been recently labelled as an oligodendroglioneural α-synucleinopathy[70, 71].

α-synuclein is a small protein, physiologically folded in tetramers, thought to contribute to synaptic vesicle transport and neurotransmitter release[58]. Adult oligodendrocytes do not normally express α-synuclein and this is also not the case in MSA[72].

In MSA, relocalization of p25α, an important stabilizer of myelin integrity, into the soma and subsequent oligodendrocyte swelling appear to be very early pathogenic steps[73]. These are followed by an increase in α-synuclein oligodendroglial concentration, possibly uptaken by neighboring neurons[74], which are unable to degrade it[75]. The interaction between p25α and α-synuclein fosters α-synuclein phosphorylation and its aggregation into insoluble oligomers first and glial cytoplasmic inclusions later on. Formation of glial cytoplasmic inclusions, in turn, activates quiescent microglial cells, which release pro-inflammatory cytokines and oxygen reactive species[76, 77]. As a result, progressively dysfunctional oligodendrocytes release misfolded α-synuclein into the extra-cellular space. In contrast to neuronal α-synuclein aggregates seen in PD, which are ribbon-shaped, α-synuclein aggregates forming in an oligodendroglial milieau are fibril-shaped and, taken up by neighboring neurons, show a higher tendency to induce neuronal cytoplasmic inclusions and cytopathological changes[78]. At this point, neuroinflammation, loss of glial-derived neurotrophic support[79] and mithocondrial dysfunction due to α-synuclein inclusions[58] synergistically promote neuronal death and subsequent reactive astrogliosis. α-synuclein toxic species may then propagate in

a prion-like fashion to other functionally connected brain areas[80] and cause the widespread neuronal degeneration typical of MSA (Figure 2).

IV. Clinical features and clinical diagnostic criteria

The onset of MSA is typically in the 6th decade of life, and occasionally between the age of 30 and 40 years (i.e. young-onset) and after the age of 75 years (i.e. late-onset)[36, 81]. Natural history studies reported a mean survival of 9.8 years with substantial variations in individual patients[8, 9]. A prolonged survival of more than 15 years has been reported in very few patients[82]. The parkinsonian variant of MSA, early onset of symptomatic OH, urinary incontinence and retention and respiratory involvement are poor prognostic factors associated with shorter survival[8, 9].

Autonomic failure

Early onset, generalized and rapidly progressive autonomic failure is typical of MSA. Rates of autonomic failure of up to 60% are reported at the disease onset (i.e. ”autonomic-first” variant of MSA)[83-85]. Erectile dysfunction is often the earliest symptom, followed by lower urinary tract symptoms and symptoms of cardiovascular autonomic failure[86]. Isolated autonomic failure in the absence of parkinsonian or cerebellar signs allows the diagnosis of pure autonomic failure. Depending on study setting, conversion rates from pure autonomic failure to MSA of up to 28% were reported within few years from disease onset[10-12]. In general, the latency to onset of symptomatic OH and urinary incontinence/retention is significantly shorter in MSA compared to PD[87] and very late onset autonomic failure has been reported in a minority of MSA patients only[82, 88].

Urinary urgency and increased frequency are common in the early disease stages, both often apparent in the first years from onset[89]. Urinary retention leads to the use of catheters in 75% of MSA patients after mean 4 years from onset[90]. In patients over 50 years of age frequent non-neurological causes of urinogenital dysfunction, like benign prostatic hypertrophy in men or pelvic floor prolapse in women, need to be ruled out[91].

Recurrent syncope in response to sudden postural trigger is a hallmark feature of OH in MSA. Less specific symptoms are dizziness, nausea, weakness, nausea and coat hanger pain (centered in the neck and shoulders in the upright position). OH is defined as a systolic/diastolic blood pressure drop of at least 30/15 mmHg upon 3 minutes of standing[15]. A common accompanying phenomenon is supine hypertension, which is defined as systolic/diastolic blood pressure increase of >140/90 mmHg measured after 5 min of rest in the supine position in a patient with OH[92]. Provoking factors, such as dopaminergic and antihypertensive medications, diuretics, dehydration, heat exposure and food intake among others may worsen the symptoms of OH in MSA patients.

The presence of OH and/or lower urinary tract symptoms might be useful to differentiate MSA-C from SAOA[93], but is usually not reliable in the differential diagnosis of MSA-P and PD at moderately advanced disease stages due to overlapping symptoms. The more aggressive disease progression may eventually suggest MSA in this setting.

Similarly, anhidrosis in MSA is widespread and progressive in contrast to asymptomatic non-progressive hypohidrosis restricted to hands and feet in PD[39, 94]. Among a number of symptoms of gastrointestinal dysfunction overlapping with PD, early severe dysphagia is peculiar for MSA[90, 95]. Pupillary autonomic involvement in MSA manifests with blurred vision, dry eyes and rarely asymmetric Adie's tonic pupil or Horner syndrome[96, 97].

Motor phenotype: parkinsonian and cerebellar features

The distinction into MSA-P and MSA-C is based on the predominant clinical features[15]. MSA-P is more common in most countries, with an exception of Japan where MSA-C is the predominant phenotype[29]. While approximately half of the patients with MSA-P develop cerebellar signs, even a higher proportion of patients with MSA-C have parkinsonian features[8, 9]. Some authors refer to the combined motor phenotype as “mixed” MSA or MSA-P+C. However, these terms are not officially accepted, because it is difficult to delineate the degree of parkinsonian and cerebellar affection in mixed clinical presentations.

Ataxia of gait, trunk and limbs, intention tremor and cerebellar oculomotor abnormalities, such as sustained spontaneous or gaze-evoked nystagmus are common in MSA. Parkinsonism is rapidly progressive, poorly responsive to L-Dopa and often associated with one or more atypical features[29]. Rapid progression to the wheelchair confinement within 5 years from symptom onset (termed also “wheelchair sign”) is present in more than a half of MSA patients, and in less than 1% of PD patients within 10 years from disease onset[90, 95]. Unilateral symptoms of parkinsonism occur in 40% of MSA patients and a similar proportion of patients retain such asymmetry over the disease course[9, 43]. A typical "pill-rolling" tremor is present in 4%-10% of definite MSA patients[43, 90]. Postural jerky tremor and/or poliminimyoclonus in the absence of "pill-rolling" tremor might be useful to distinguish MSA from PD[81]. Early postural instability and gait difficulties coupled with falls are suggestive of atypical parkinsonism rather than PD[89, 98]. Latency to onset of recurrent falls in MSA is significantly shorter compared to PD and longer compared to PSP[99]. Camptocormia, Pisa syndrome and disproportionate antecollis are common postural deformities in MSA (Table 1)[95].

Patients with MSA have an early, usually transient, and in general poorer, response to L-Dopa compared to patients with PD. Beneficial L-Dopa response was observed in 42%-57% of MSA-P and 13%-25% of MSA-C patients in the natural history studies[8, 9]. However, a "dramatic" L-Dopa responsiveness, as stated in the diagnostic criteria for PD[100], could be fulfilled only by a small minority of MSA patients. Side effects induced by the acute L-Dopa challenge test are also more frequent in MSA compared to PD patients[101]. L-Dopa induced dyskinesias (dystonic>choreatic, primarily affecting craniocervical region) and fluctuations are observed in 27% and 24% of definite MSA patients, respectively[81].

Red flags

The presence of multiple red flags highly specific for MSA in the context of adult-onset progressive parkinsonism, ataxia or autonomic failure may provide important clues for a correct and early diagnosis (Table 1)[95]. In the recent clinicopathological study on 203 clinically diagnosed MSA patients, a lifetime recorded number of red flags was higher in both MSA-P and MSA-C compared to Lewy body disease and PSP[90, 95]. Nevertheless, no differences were found in the frequencies of red flags within 3 years from disease onset between MSA and MSA lookalikes[90].

Other non-motor and motor features

RBD is a premotor symptom of an evolving α-synucleinopathy and, as such, is not peculiar to MSA. The frequency of RBD increases with disease duration, with an estimated lifetime prevalence in patients with MSA of 90-100%[102]. A significant proportion of patients with an isolated RBD later progress to MSA[13, 103]. Depending whether clinical presentation is parkinsonian or cerebellar, the presence of RBD is useful for the differential diagnosis

between MSA, SAOA and tauopathy, but not among α-synucleinopathies. New onset of snoring, sleep fragmentation, obstructive sleep apnea and restless leg syndrome are other nocturnal problems in MSA.

Laryngeal stridor occurs in up to one third of MSA patients and is a very uncommon presenting symptom of the disease. When stridor occurs early, it is more frequent in the autonomic-first variant of MSA and is considered an unfavorable predictor of survival, posing patients at higher risk of sudden death during sleep[85]. Stridor develops after a selective paralysis of the vocal cord abductor, glottis narrowing and laryngeal dystonia[40].

Approximately 30% of MSA patients show cognitive impairment most frequently in a form of mild frontal executive dysfunction[43, 104]. However, major cognitive dysfunction is not typical of MSA, in contrast to other differential diagnostic entities featuring various degrees of dementia, such as DLB, PD with dementia and PSP[15].

Moderate to severe depression affects up to 50% of patients with MSA and an even higher proportion of patients have milder symptoms[105]. Common depressive symptoms are sadness, hopelessness, fatigue and decreased satisfaction[105]. Other mood disturbances in MSA are apathy, anxiety[44] and dysregulation of emotional expression, which is also a red flag supporting a MSA diagnosis (Table 1). By contrast, hallucinations are present in only 9%-13% of MSA patients[43, 106].

Sensorimotor axonal neuropathy, present in up to 40% of patients, mostly manifests with sensory disturbances[107]. Pain, reported by at least 80% of MSA patients, occurs in a form of rheumatic, sensory, dystonic and levodopa-related pain[108, 109].

Unintelligible speech, resulting from the combination of cerebellar, extrapyramidal (dystonic and myoclonic) and spastic dysarthria, arises in approximately half of patients with MSA after 6 years from onset[90]. MSA-P patients often develop a high-pitched, quivery and croaky voice, whereas MSA-C patients often have scanning dysarthria. Hyperreflexia and Babinski sign are present in up to 60% and 40% of MSA patients, respectively[8, 9].

Olfactory dysfunction is a common finding in patients with PD [110, 111]. In fact, prospective studies in idiopathic RBD suggest that hyposmia may even be a symptom of prodromal PD[112, 113]. In contrast, olfactory function remains largely intact in atypical parkinsonian disorders including MSA [114-121] and assessment of odor identification can support the differential diagnosis [122]. The recently revised diagnostic criteria for PD consider olfactory loss (i.e. olfactory testing in the anosmic or clearly hyposmic range) as a supportive criterion for the diagnosis of PD [100].

Diagnostic criteria

In the current set of consensus criteria[15] probable MSA is the highest and possible MSA the lowest level of clinical diagnostic certainty (Table 2)[15]. A diagnosis of probable MSA is based on clinical features, while ancillary diagnostic tests including magnetic resonance imaging, positron emission tomography and single-photon emission computed tomography support a clinical diagnosis of possible MSA[15]. In a validation exercise, the sensitivity of the 2nd consensus criteria was 41% for possible and 18% for probable at first clinical visit, and 92% and 63% at last clinical visit respectively[123]. Among patients diagnosed with MSA during life only 62% and 79% met the pathological criteria for MSA in two recent brain bank studies from

the Queen Square Institute in London, UK and from the Mayo Clinic in Jacksonville, USA[43, 90]. The most common misdiagnoses in the Queen Square brain bank study were DLB in 13% and PSP in 6% of patients[90]. In the Mayo Clinic Jacksonville cohort, MSA was most frequently misdiagnosed as DLB in 14%, PSP in 11% and PD in 6% of patients[43]. There are several issues possibly explaining the suboptimal diagnostic accuracy of the current criteria[69]. Therefore, the 3rd revision of MSA diagnostic criteria was initiated in 2018 by G. K. Wenning and H. Kaufmann under the auspices of the International Parkinson and Movement Disorder Society. This will ideally allow earlier and more accurate diagnosis of MSA based on the recent advances in neuroimaging and biomarker research.

V. Diagnostic biomarkers

Numerous imaging studies (MRI, radio-tracer imaging, cardiac imaging)[124-134] as well as blood and tissue biomarker studies[135-141] explored the differential diagnostic potential of these different methods to reliably discriminate MSA from related disorders including PD and sporadic, adult-onset ataxias. A detailed summary of available diagnostic imaging markers is provided in Table 4. While numerous studies were performed in cohorts of patients with degenerative parkinsonism, only a minority of the studies assessed the diagnostic potential of biomarkers for the differential diagnosis of MSA versus sporadic adult-onset ataxias.

Cerebral magnetic resonance imaging

A comprehensive review on the diagnostic yield of MRI in neurodegenerative parkinsonism was published recently[142]. The underlying neuropathological changes with cell loss, microglial

as well as astroglial activation can be visualized using different MRI modalities. These include regional volume changes, T2- and diffusion-weighted MRI signal changes and increased iron deposition. In general, there is insufficient evidence for the differential diagnosis of MSA versus sporadic adult-onset ataxias using MRI. In neuropathologically confirmed MSA and PSP cases the overall sensitivity of a radiologically-supported diagnosis of MSA or PSP based on conventional MRI sequences was 77% and 73%, respectively with no PSP case misclassified as MSA or vice versa[143]. Several MR abnormalities (putaminal and posterior fossa changes; figure 3) were reported to be specific for MSA (reviewed in detail in [125]). Significant brain atrophy has been reported in the putamen[144-150], the middle cerebellar peduncles (MCPs)[146, 151], the cerebellum[146] as well as in several brainstem regions including the pons, medulla oblongata and the midbrain[145, 146, 151]. Signal increases on T2 weighted sequences (figure 3) including the "hot cross bun" sign (a cruciform hypointensity in the pons), the "MCP-sign" (i.e. hyperintensitiy in the MCP) and the "putaminal slit" sign (hyperintense signal in the dorsolateral margin of the putamen) were reported to have high positive predictive values for the diagnosis of MSA[152, 153]. However, while putaminal atrophy appears to discriminate MSA from PD satisfactorily, one has to be cautious in terms of intensity changes since these are tightly correlated with the magnetic field strength. In fact, a hyperintense putaminal rim is a common finding in healthy adults at 3T MRI[154]. On the other hand putaminal atrophy together with hypointense putaminal signal changes on iron-sensitive routine sequences (figure 3) such as T2* or susceptibility weighted imaging (affecting typically the posterior part of the putamen) seem to be specific for MSA-P[142, 155, 156]. Finally, the "hot cross bun" sign is only a surrogate of ponto-cerebellar atrophy and was reported in patients with secondary parkinsonism due to vasculitis[157] as well as in patients with genetically confirmed spinocerebellar ataxia type 2 and 3[158, 159]. Overall, although the sensitivity of MR atrophy

patterns is far from satisfactory, especially in early disease stages, the specificity of these MRI abnormalities differentiating MSA from PD is high.

Apart from visual interpretation of MRI, MR volumetry with (semi-)automatic segmentation techniques have become increasingly popular in recent years [142]. Two recent meta-analyses [160, 161] including voxel-based morphometry (VBM) studies that enrolled patients with atypical parkinsonian disorders identified distinct atrophy patterns in patients with MSA or PSP as compared to PD. While there were no significant differences in gray matter volume loss between PD patients and controls[160, 161], patients with MSA-P and PSP showed regions of atrophy distinctive to each disease[160, 161], including putamen and claustrum in MSA-P, as well as the thalamus, midbrain and insula in PSP with mild overlap of GM volume loss between PSP and MSA-P[161]. However, since VBM is based on group-wise comparisons, it cannot be exploited for the differential diagnosis at the single-patient level[162] and, thus, more recent automated image segmentation techniques attempted to characterize regional brain volume loss at the individual patient level. Such approaches yielded high diagnostic accuracy for discriminating patients with MSA from related movement disorders with putaminal and MCP atrophy being shown to be useful in separating MSA from PD[148-150]. Other quantitative measures include brainstem area and cerebellar peduncle widths measurements that can be manually obtained in clinical practice with a high reproducibility [142]. The MR parkinsonism index (MRPI; [area pons/area midbrain] x [width MCP/width SCP]) is able to differentiate PSP patients from non-PSP parkinsonism including PD and MSA as well as healthy controls[129, 163, 164]. Both a decreased m_a/p_a-ratio as well as an increased MRPI seems to distinguish PSP from MSA, PD, and healthy controls. On the other hand, a MCP diameter <8.0 mm has not only

optimal diagnostic accuracy in separating MSA from PD[165], but seems also to discriminate MSA from PSP with fairly acceptable diagnostic accuracy[164].

Differences in putaminal diffusivity (figure 3) are particularly helpful for the differential diagnosis of MSA-P vs. PD with patients being discriminated with high sensitivity and specificity[166]. However, putaminal diffusivity measures overlap between MSA and PSP patients [167, 168], hence, additional imaging measures such as volume changes or increases in diffusivity within the posterior fossa need to be introduced to reliably separate MSA from PSP. Intriguingly, conflicting results were reported for diffusivity changes in the MCP – some studies reported a high diagnostic accuracy for MSA-P [168, 169], whereas others were unable to confirm this finding [170, 171].

Although quantitative putaminal changes on iron-sensitive MRI sequences are common in MSA patients, individual study results vary considerably and no overall conclusion can be drawn yet [142].There is preliminary evidence of distinct topographical patterns of abnormal subcortical brain iron accumulation in patients with PD, MSA and PSP involving the putamen in MSA-P and PSP, as well as red nucleus, dentate nucleus, globus pallidum and thalamus in PSP with overlapping patterns between PSP and MSA patients[142]. However, large-scale confirmative studies remain to be performed.

Several studies [172-176] assessed the diagnostic potential of multimodal MRI. These studies commonly include a combination of volumetric, diffusion-weighted imaging measures and iron-sensitive MR measures. Various combinations were exploited for the development of diagnostic algorithms and these machine-learning-supported algorithms yield good to excellent diagnostic accuracy. However, these approaches remain investigational and are restricted to highly specialized centres.

Radio-tracer imaging

Presynaptic dopaminergic denervation along the nigrostriatal pathway was demonstrated in numerous studies of neurodegenerative parkinsonian disorders. All of these studies were unable to identify a clear-cut difference between PD and atypical parkinsonian disorders based on nigrostriatal presynaptic dopaminergic imaging. However, some studies suggest that PD can be satisfactorily discriminated from atypical parkinsonian disorders by extrastriatal (i.e. brainstem) presynaptic dopamine denervation and distinct patterns of striatal dopaminergic denervation[177-181]. Nigrostriatal presynaptic dopaminergic denervation is not only a typical finding in MSA-P patients, but has also been observed in a substantial proportion of MSA-C patients [182] and, in 43% of patients with MSA-C, nigrostriatal presynaptic dopaminergic denervation preceded a clinical diagnosis based on consensus diagnostic[183]. There is also preliminary evidence that presynaptic dopaminergic imaging can discriminate patients with MSA-C from sporadic, late-onset ataxias [182], although markedly reduced FP-CIT binding was reported in SCA2 patients[184].

The diagnostic utility of post-synaptic dopamine receptor imaging (figure 3) was studied in several small scale studies exploiting different radio-tracers (see Table 4) and different modalities (PET, SPECT)[185-191]. Patients with MSA or PSP regularly showed reductions in putaminal dopamine D2 receptor binding, whereas this was normal or slightly elevated in PD patients. Hence, patients with neurodegenerative parkinsonism were correctly assigned to the “atypical parkinsonian disorders” category, however, postsynaptic dopamine imaging was unable to discriminate atypical parkinsonian disorders from one another.

A number of FDG-PET studies evaluated the pattern of resting regional glucose metabolism in neurodegenerative parkinsonian disorders. Cerebellar, brainstem and striatal glucose metabolism was commonly reported to be altered in patients with MSA. A recent systematic review even demonstrates that the specificity of FDG PET for diagnosing MSA was consistently above 90% in the different studies, whereas the sensitivity was more variable (but greater than 75% in all instances)[192]. More sophisticated, automated image-based classification exploiting pattern analysis was able to accurately diagnose MSA in independent cohorts suggesting that this approach is useful for the differential diagnosis of MSA[193-195]. There is, however, insufficient evidence for the discrimination versus sporadic adult-onset ataxias.

Cardiac sympathetic innervation can be visualized using different tracers (see table 4) with the most commonly used tracer being the ^{123}I-labelled noradrenalin analogue MIBG (figure 3). Although most MIBG scintigraphy studies demonstrated that myocardial sympathetic innervation was normal in MSA patients, mildly reduced sympathetic innervation has been reported in some cases[196-198]. In contrast, multiple imaging studies with MIBG in PD patients have shown decreased cardiac uptake, indicating myocardial postganglionic sympathetic dysfunction, even when cardiovascular reflexes remain intact[196-198]. However, in early stages of PD, MIBG uptake can be normal[199]. Overall, recent meta-analyses suggest that MIBG imaging is useful to discriminate PD from MSA in moderate to advanced disease stages, but unreliable in early stages since early stage PD patients may have a normal cardiac sympathetic innervation[196-198]. Moreover, MSA cannot be discriminated from PSP based on MIBG scintigraphy alone[200].

Transcranial sonography (TCS)

In the differential diagnosis of sporadic parkinsonism, normal echogenicity of the substantia nigra argues against a diagnosis of PD, rather suggesting the presence of a drug-induced or atypical parkinsonian disorder such as MSA[201, 202]. Overall, TCS is an easy to implement, non-invasive, and inexpensive technique that could help in the early differential diagnosis of PD versus other parkinsonian syndromes including MSA[201, 202]. However, the diagnostic utlility in discriminating atypical parkinsonian disorders from one another is limited, despite recent studies suggesting that dilated 3rd ventricle width is of additional value in separating PSP from MSA[203]. It needs to be acknowledged that a missing temporal bone window is present at least 10% of patients.

Blood and tissue biomarkers

In recent years, there was an increasing interest in research on diagnostic biomarkers derived from body fluids [i.e. blood plasma and cerebrospinal fluid (CSF)]. α-synuclein levels have been measured in CSF and plasma of PD patients[204, 205] as well as in MSA patients[206-208] reporting decreased CSF α-synuclein levels in MSA and PD compared to age-matched controls. These observations suggest that CSF α-synuclein is not useful for the distinction between different synucleinopathies. Regarding the usefulness for the discrimination between MSA and PSP, study results remain contradictory.

The early detection of fibrillary aggregates of α-synuclein in peripheral tissues samples (e.g., gastrointestinal tract mucosa, salivary glands, skin) is considered a potential biomarker for identifying synucleinopathies[135, 209]. Among the peripheral tissues that have been studied in

synucleinopathies, the skin appears to be one of the most promising diagnostic marker not only for PD, but also for MSA[135]. A major advantage of skin biopsies compared to biopsies from other tissues is that it is an easily accessible organ, and as such suitable for both single and repeated sampling[135]. When looking at the class of nerve fibers affected in skin biosies, studies involving patients with MSA found α-synuclein accumulations mainly in unmyelinated somatosensory fibers of the subepidermal plexus but not in dermal autonomic fibers, while in patients with Lewy body diseases they were observed mainly in autonomic fibers of the skin[135]. Overall, the diagnostic accuracy among different studies vary considerably and additional confirmatory studies are required to establish skin biopsies as reliable diagnostic biomarker for MSA[136, 210-212]. The major source of heterogeneity were methodological differences including the site of biopsy, tissue thickness, differences in pre-analytics and the selection of antibodies (e.g. polyclonal versus monoclonal; total α-synuclein versus phosphorylated α-synuclein) for staining and quantification of α-synuclein deposits[135]. Intriguingly, there is preliminary evidence of absence of phosphorylated α-synuclein deposits in skin biopsies of patients with 4R-tauopathies such as PSP[212], suggesting that this might become a reliable marker for discriminating synucleinopathies from 4R-tauopathies.

While studies have also consistently reported higher CSF neurofilament light chain (NFL) levels in MSA compared to PD and healthy controls[213-221], CSF NFL concentrations between atypical parkinsonian disorders were not different in the majority of studies[213-216, 220, 221].

The most promising approaches exploit biomarker “panels” (i.e. a combination of different biomarkers) to discriminate between MSA and related disorders[215, 216, 219, 220, 222-225]. The most frequently studied proteins in these panels are tau, phospho-tau, α-synuclein and NFL. Intriguingly, these early studies in relatively small cohorts suggest a high sensitivity and

specificity of these biomarker panels. However, large-scale, multicentric validation studies are missing and it remains to be seen whether the results of these small-scale studies can be replicated in large-scale, multi-centre studies.

VI. Current treatments

Parkinsonism - pharmacotherapy

The 1st line treatment of a hypokinetic-rigid phenotype is dopaminergic treatment with levodopa. However, a poor levodopa response is characteristic to the extent of a diagnostic feature of possible and probable MSA-P[15]. Approximately one third of patients may respond to levodopa, although benefit is temporarily limited and compared to patients with PD the effect is often markedly reduced[226-228]. Levodopa response may be considered positive by improvement of 30% or more on the motor examination (ME, - part II) of the UMSARS[229]. Overall, the use of levodopa relies on a broad clinical experience, but there is low evidence. Even though data on levodopa effect is limited, unresponsiveness to levodopa should only be accepted after a treatment period of at least 3 months in daily doses of up to 1 g[230] without any significant clinical improvement[15]. In cases with unclear response, withdrawal of medication may lead to a deterioration and justify continuation of treatment[29]. Dopamine agonists are not considered a therapeutic option, as they show poor efficacy and may involve severe side effects, particularly worsening of OH[230, 231].

Amantadine may be considered as an alternative or additional treatment option for parkinsonism (2–4x 100 mg daily). However, also for amantadine, the evidence is weak. In anecdotal reports a trend towards reduction of motor symptoms seemed to be present, but

a placebo-controlled trial did not show a clinically significant antiparkinsonian effect[228, 232, 233]. Side effects therefore need to be considered very carefully in the evaluation of treatment effects. Side effects may include leg edema, livedo reticularis and confusion[234].

Cerebellar syndrome - pharmacotherapy

For cerebellar symptoms such as gait ataxia, scanning dysarthria, ataxia of the limbs, intention tremor and oculomotor dysfunction, no efficient drug treatment is available. Anecdotal reports describe beneficial effects of aminopyridine on cerebellar symptoms[235].

Dystonia - pharmacotherapy

Focal dystonia, e.g. blepharospasm, cervical dystonia (especially disproportionate antecollis), and limb dystonia, is common in MSA with a prevalence between 12% and 46%[81, 236]. Botulinum toxin injections are described to be effective in the treatment of blepharospasm and may reduce symptoms of dystonic limbs[237]. However, treatment of cervical dystonia with botulinum toxin injections is being regarded as potentially harmful, as severe dysphagia very rarely may occur[238].

Movement disorders – non-pharmacological therapy

Non-pharmacological treatment options such as physiotherapy and occupational therapy play important roles in improving symptoms and patient's quality of life. This is even more true as the effect of symptomatic therapy is mostly limited. As for pharmacological interventions aiming at Parkinsonism, also for non-pharmacological interventions evidence is limited. However, a randomized-controlled trial of patients with mild to moderate MSA obtaining occupational therapy showed significant improvement of motor function and activities of daily life[239]. Evidence is available regarding improvement of motor function by

physiotherapy in Parkinson's disease[240], but no controlled trials for physiotherapy in MSA are available so far. However, single reports suggest that predominant Parkinsonism as predominant motor feature may also benefit from physiotherapy[241]. In degenerative cerebellar disorders, intensive physiotherapy as well as resistance training and challenge-oriented gait and balance training may improve coordination, balance and gait[235, 242-245]. Even though no specific data for MSA are available, physiotherapy aiming at the cerebellar component is often integrated in the therapeutic concept. Furthermore, patients with cerebellar dysarthria and impairment of swallowing may benefit from speech therapy[241].

Physical support including canes, walkers or wheelchairs will be an option to support patients with severe movement disorders provided that patients are capable of using them.

Deep brain stimulation

In PD, deep brain stimulation (DBS) has been used very efficiently to improve motor symptoms such as hypokinesia and tremor as well as motor complications leading to an improved quality of daily life[246, 247]. The role of DBS for the treatment motor symptoms in MSA has not been studied in controlled trials. The limited evidence for DBS in MSA is derived from case reports and series[248, 249]. A review of the literature including 26 patients with MSA (12 autopsy-confirmed MSA patients) who underwent DBS surgery, however, highlights the poor efficacy of DBS for the treatment of motor symptoms in MSA[250]. Although DBS may improve motor symptoms in MSA patients, especially in those with preserved levodopa-response, motor improvement after surgery is typically short-lived and rapidly counteracted by the occurrence of disabling MSA symptoms[250]. Intriguingly, in one case series, about one quarter of patients died within one year of surgery[250]. Overall, based on the limited evidence

from the literature, DBS cannot be recommended in MSA as suggested by poor outcome and the possibility of harmful adverse effects[249, 250].

Autonomic failure

All MSA patients diagnosed using the current diagnostic criteria experience autonomic symptoms since these are a mandatory feature in current diagnostic criteria of MSA (see above). In detail, a wide variety of non-motor symptoms can be present at a time[251], with autonomic symptoms being the most important group of symptoms. It has been shown that non-motor symptoms correlate strongly with quality of life, much more than motor symptoms[252]. To assure appropriate therapy, non-motor symptoms deserve special attention during the assessment of the patients.

Urge incontinence caused by detrusor hyperreflexia and sphincter detrusor dys-synergy may be alleviated by applying anticholinergic substances like oxybutinine (2–3x 2.5–5 mg/d) or trospium chloride (1-2 x 15mg/day)[29, 241]. However, anticholinergic treatment leads to an increased risk of worsening urinary retention and cognitive decline: this is less likely with anti-cholinergics not crossing the blood-brain barrier, like trospium. Alternatively, beneficial effects of botulinum toxin injections into the detrusor muscle have been described in single cases with detrusor over-activity[242, 253]. In case of nocturia, again single cases reported positive response to desmopressine (5 µg intranasal spray at night) without any observed side effects[254, 255]. Neurogenic incomplete bladder emptying may cause significant morbidity due to consecutive urinary tract infections. If feasible, clean intermittent self-catheterization is recommended as first-line treatment[256]. Due to motor impairment permanent suprapubic

catheterization may be necessary in advanced disease stages. As an alternative, drug treatment with urethra-oriented alpha-adrenergic antagonists such as tamsulosin (0,4 mg/day), prazosin (3x 1 mg) and moxisylyte (3x 10 mg) can be added, even though risk of worsening OH has been reported. Therefore, clinical use should be limited to patients unable to perform self-catheterization.[29]

For the treatment of erectile dysfunction sildenafil has been proven to be efficacious in studies of high quality[257, 258]. However, treatment can cause serious side effects in form of exacerbation of orthostatic hypotension. Therefore, the use of sildenafil in MSA should be approached with caution.

For OH – comparable to many other symptoms – a combination of pharmacological and non-pharmacological interventions might provide best symptom control. Non-pharmacological treatment options include elastic stockings, abdominal bands, adequate intake of salt and fluid and avoiding exposure to hot, humid environments. Also, postural maneuvers such as head-up tilt during the night to increase intravasal volume and reduce hypotension in the morning[230, 259-263]. Available drugs for pharmacological treatment include sympathomimetics such as the well-studied midodrin (3 x 2.5–10 mg)[264], the norepinephrine precursor L-threo-3,4-dihydroxyphenylserine (L-DOPS 200 - 2000 mg daily, recently FDA approved)[265] and other drugs such as ephedrine (3 x 15–45 mg) with no explicit MSA trial data[266]. The durability of the improvement caused by sympathomimetics beyond 2 weeks has not been demonstrated[267-269]. An alternative and widely used drug is fludrocortisone (0.1–0.4 mg/day) even though it has not been explicitly studied for MSA, but data is available for PD[270, 271].

Postprandial hypotension may also be addressed by pharmacological and non-pharmacological measures such as small and frequent meals with low carbohydrate content and octreotide (25–50 µg s.c. 30 min before meals)[272, 273].

Neuropsychiatric manifestations

Depression and anxiety are frequent symptoms in MSA, also cognitive impairment affects up to 30% of the patients. For the treatment of anxiety and depression, a combination of cognitive behavioral therapy as well as selective serotonergic reuptake inhibitors with lower risk of orthostatic hypotension than tricyclic drugs are primarily recommended. Alternative treatments with very low evidence that has been described in MSA cases fulfilling psychiatric criteria for major depression includes electroconvulsive therapy[274]. Cognitive impairment of patients with MSA usually affects predominantly processing speed and executive functions suggesting a predominant fronto-subcortical pattern of cognitive dysfunction[275]. To date, no effective treatment of cognitive impairment is available.

Sleep disorders

RBD affects 90–100% of MSA patients[29]. However, no treatment trial of RBD in MSA has been performed so far. Treatment recommendations of RBD in MSA rely on general RBD recommendations. Clonazepam (0.5-2 mg) and Melatonin (2-5mg) should be considered for the treatment of RBD[276, 277].. Often small doses of Clonazepam 0.25 – 0.5 mg are sufficient. Melatonin can be combined with Clonazepam and should be the first line choice in case clonazepam is not efficient/contraindicated[278].

Nocturnal stridor is a frequent symptom in MSA associated with respiratory failure and sudden death during sleep[279, 280]. Small studies support the use of home non-invasive positive

pressure ventilation (NPPV)[281] and continuous positive airway pressure (CPAP) ventilation[282]. Tolerability of this kinds of treatment is well, especially early in the disease[283].

VII. Unmet Needs and Future Treatments

The most urgent unmet need for MSA, as well as for most neurodegenerative diseases, is the development of a treatment option that would be able to modify the clinical disease course. Past attempts to modify the clinical disease course have not been successful so far and are listed in "striving for a cure" (see above). Currently, we face interesting times in which MSA has received increased attention of scientists and companies working on a therapy that aims at modifying the clinical disease course[284, 285]. To increase the chance of success of the development of interventions that modify the clinical disease curse, several recommendations have recently been made by a panel of international experts. These recommendations cover amongst other topics clinical outcome measures and biomarker development[285].

Besides this most urgent topic, development of symptomatic treatment for an effective relieve of all symptoms including movement disorders is another urgent need[284].

Recently, reasonable and science-based criticism of the current diagnostic criteria (see above) has been expressed[69]. On this basis, a revision has been started.

Finally, a topic of pivotal importance is the need to raise disease awareness. Work of tremendous value is on-going by several organizations. Recommendations regarding the increase of knowledge amongst healthcare professionals, the public and to foster collaborative networks at several levels have recently been presented[285].

Figure legends

Figure 1 – The MSA historical milestones.

Figure 2 – The etiopathogenesis of MSA. From A. Fanciulli and G. K. Wenning, Multiple system atrophy, NEJM, 372(3): 249-63; Copyright © 2015 Massachusetts Medical Society. Reprinted with permission.

Figure 3 - Imaging methods used to study MSA.

Part 1: Midsagittal T1-weighted images showing Infratentorial atrophy (pons and cerebellum; dilated forth ventricle) (arrow – pons) in a patient with MSA (a) and the hummingbird sign (arrow) (atrophy of the rostral midbrain tegmentum) in a patient with PSP (b), while there is no relevant brainstem atrophy in a patient with PD (c). *Part 2:* "Hot cross bun" sign (arrow) in a patient with MSA on T2-weighted images. *Part 3:* Putaminal changes (atrophy, hyperintense rim, putaminal hypointensity in comparison with the globus pallidus) (arrows) at both sides in a patient with MSA (a) on T2-weighted images compared to a patient with PD (b) having no basal ganglia abnormalities. *Part 4:* atrophy of MCP with the MCP-sign (hyperintensity in the MCP) (arrows) on T2-weighted images in a patient with MSA (a) compared to a PD patient (b). *Part 5:* Note the diffuse hyperintensity (corresponding to increased diffusivity values) in the posterior part of both putamina (arrows) in a patient with MSA (a) compared to a PD patient (b) on DWI. These changes in the MSA patient were observed only 6 months after onset of levodopa responsive parkinsonism with an anticipation of 18 months in relation to the clinical diagnosis of possible MSA-P and of 24 months for the diagnosis of probable MSA. *Part 6:* Putaminal atrophy and putaminal hypointensity (arrows) on SWI in a patient with MSA (a) compared to

a PD patient (b). As in this MSA patient, putaminal hypointensity start typically in the dorsolateral part of the putamen. *Part 7:* Planar cardiac delayed ^{123}I-MIBG imaging in a patient with MSA (a) compared with a patient with early PD (b). There is markedly reduced MIBG uptake in the heart (H) in the patient with PD compared to the mediastinum (M). *Part 8:* Post-synaptic dopaminergic imaging with ^{123}I-IBZM SPECT shows normal striatal tracer uptake in a PD patient (b), while in the MSA (a) patient there is reduced asymmetric striatal (arrows) tracer uptake with more marked reduction in the left.

Abbreviations: DWI= diffusion-weighted imaging; IBZM= iodobenzamide; MIBG= metaiodobenzylguanidine; MCP= middle cerebellar peduncle; MSA = multiple system atrophy; PD = Parkinson's disease; SWI = susceptibility-weighted imaging

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