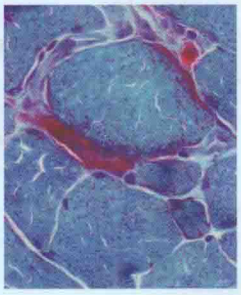
Edited by Néstor Gálvez-Jiménez, and Paul Tuite

Uncommon Causes of MOVEMENT DISORDERS



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Uncommon Causes of Movement Disorders

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To
Kassandra, Jessica, Nicholas, Luis and Cara Galvez.
My parents.
Ms. Pauline M. Braathen.
Néstor Gálvez-Jiménez

To
My wife Marilee, children John and Audrey along with siblings Clare, Ann, Frances, Brian and Kathy, and my parents John and Camille.
Paul Tuite

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Preface

This book came about when it became clear that a work on unusual movements or unusual causes of disorders of motor control was lacking, especially for neurologists, neurosurgeons and psychiatric specialists and physicians in training. Most available books are almost exclusively for movement disorders specialists; or the information related to these conditions is found scattered throughout the literature. In addition, many aspects related to movement disorders such as neuro-ophthalmologic problems, demyelinating diseases, neuromuscular disorders, gait and balance difficulties and the boundaries of epilepsy and neuropsychiatric diseases are beginning to be recognized as important in the field but are poorly discussed in most textbooks. We cover these areas extensively in this book. Along with our publishers we hope this work can begin to fill the gap. The book follows a sequence beginning with akinetic rigid syndromes and followed by hyperkinetic and miscellaneous disorders. With advances in the field, the scope of movement disorders now includes disorders of gait and balance, cerebellar conditions, dementing disorders with "extrapyramidal" signs, disorders of sleep, and movement conditions that overlap neuromuscular diseases or epilepsy conditions. Examples of such include cramps, fatigue, weakness, twitchy muscles/fingers/extremities, nocturnal jerks and movements, hypermotor behaviors and disorders of sleep.

The book features chapters on multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration written by the teams headed by Professors Gregor Wenning, Carlos Singer and David Riley, respectively, who have been pioneers in the understanding of these disorders. The emerging area of apraxias in movement disorders was superbly written by Roneil Malkani and Cindy Zadikoff. Wilson disease is reviewed by Dr. Neeraj Kumar from the Mayo Clinic, in which he demonstrates his expertise in the diagnosis and treatment of such conditions. Continuing progress in neurodegeneration with brain accumulation is reviewed by Dr. Paul Tuite and Mr. Bower from the University of Minnesota. In this review, the authors make simple to the reader what is normally a complex disorder and demonstrate their accumulated expertise in this group of disorders. Dementia with parkinsonism and impulsive and compulsive behaviors are reviewed by Drs. Praveen Dayalu and Kelvin Chou, and by Drs. Nelson Hwynn and Hubert Fernandez, respectively.

We were extremely lucky to have Professor Kurt Jellinger revisit pallidal and thalamic atrophies, a topic that was last reviewed by him many years ago in the *Handbook of Neurology* edited by Bruyn. This timely review puts into current perspective the advances in this rarely discussed area. Professor Alberto Albanese and Professor Giacomo Dell Marca introduce us to restless legs syndrome and sleep-related disorders, areas in which both authors are very well known. Professor Christine Klein has made seminal contributions to the understanding of genetics in movement disorders. She and her team provide an up to date introduction to dystonic syndromes, focusing on the emerging genetics of dystonia.

Other dyskinesias such as hemifacial spasm, tardive dyskinesias and other drug-induced movement disorders are reviewed in detail by Danita Jones and Néstor Gálvez-Jiménez of the Cleveland Clinic in Florida and Santiago Perez-Lloret and Marcello Merello from Buenos Aires, Argentina, respectively. Drs. Jones and Gálvez-Jiménez introduce us to a practical anatomy of the facial nerve, its pathophysiology and unusual causes of hemifacial dyskinesias. Professors Perez-Lloret and Merello provide the reader with a practical overview of drug-induced movement disorders and tardive syndromes.

Nonhereditary choreas and neuroacanthocytosis are introduced by two very well-recognized experts in the field. Dr. Francisco Cardoso from Brazil reviews his experience in nonhereditary choreas, and Dr. Ruth Walker from New York presents her experience in neuroacanthocytosis.

Tremor and myoclonus are superbly reviewed by Drs. Mark Stacey and Julia Johnson and by Drs. Steven Frucht and Era Hanspal, respectively. Dr. Stacey's and Dr. Frucht's groups have made seminal contributions in movement disorders, especially in tremor and myoclonus. We were very fortunate to have them participate in this project.

Dr. Roger Kurlan's expertise in tics and Tourette syndrome is demonstrated in his review of the topic. The complex area of cerebellar disorders is superbly covered by Dr. Susan Perlman and her team from UCLA. Unusual gait disorders and psychogenic movement disorders are discussed by Dr. Victor Fung and Mr. Samuel Kim from Adelaide Australia and by Dr. Alberto Espay from Cincinnati, Ohio.

Stiff person syndrome is reviewed by Dr. Daniel Sa from the Marshfield Clinic. Hereditary spastic paraplegias are summarized by Drs. Ramon Lugo, Taranum Khan and Néstor Gálvez-Jiménez from the Cleveland Clinic in Florida and by Mr. Matthew Bower from the University of Minnesota.

Miscellaneous disorders that overlap other areas of neurology including cramps, contractures and myalgias are covered by Drs. Virgilio Salanga and Michelle Dompenciel, neuromuscular clinicians with extensive expertise in the field and in general neurology. This chapter represents the twilight zone between neuromuscular diseases and movement disorders. Similarly, the boundaries between epilepsy and movement disorders are continuously being revised in the light of novel information about cortical and deep brain structures such as the basal ganglia and thalamus. This area is succinctly reviewed by Drs. Selim Benbadis and Eissa Ibrahim Al Eissa. Dr. Benbadis's team from Tampa has made numerous contribution to the field of epilepsy, abnormal movements and psychogenicity.

In addition, neuro-ophthalmologic alterations in patients with movement disorders are reviewed by authorities in the field such as Professors Jan Kassubek and Elmar Pinkhardt; while cerebrovascular diseases and movement disorders, and demyelinating diseases resulting in abnormal movements are covered by Professor Jose Biller and his team from Loyola University, and by Dr. Daniel Kantor from Gainsville, Florida, respectively. These three topics complete the miscellaneous movement disorders that are rarely discussed and summarized in a work of this nature.

As editors we found the preparation of this work a very humbling experience and daily lessons were learned during the preparation and coordination of the work. We are extremely grateful to all contributors for their willingness to take the time from busy personal and professional lives to write these papers summarizing their area of expertise and for their patience during the preparation of this work.

Finally. N. G.-J. would like to thank Ms. Pauline Braathen and the Pauline Braathen fund for their unyielding support of his activities. None of this work would have been possible without their support.

Néstor Gálvez-Jiménez
Paul Tuite

Contents

Chapter 1

Multiple system atrophy

Sylvia Stemberger and Gregor K. Wenning

History

Multiple system atrophy (MSA) is a progressive neurodegenerative movement disorder characterized by a variable combination of autonomic failure, poorly levodopa-responsive parkinsonism, cerebellar ataxia and pyramidal symptoms. Neuronal cell loss in the basal ganglia, cerebellum, pontine and inferior olivary nuclei, pyramidal tract, intermediolateral cell column and Onuf's nucleus as well as gliosis and α-synuclein containing glial cytoplasmic inclusions (GCIs) are typically observed [1]. MSA is an orphan disease (prevalence rate 4.4/100 000; incidence rate 3/100 000 per year [2,3]) equally affecting men and women; it usually starts in the sixth decade and progresses relentlessly, with death occurring after an average of 9 years [4].

Up to 1969, three cardinal presentations of MSA including striatonigral degeneration (SND), sporadic olivopontocerebellar atrophy (OPCA), and the Shy–Drager syndrome (SDS) were regarded distinct entities until Graham and Oppenheimer recognized their substantial clinicopathological overlap and proposed MSA as umbrella term [5]. Ubiquitin-positive GCIs were first reported in 1989 [6] and subsequently confirmed as cellular marker of MSA regardless of the phenotypic presentation. α-Synuclein immunostaining of GCIs was first described in the late 1990s. Following this discovery, MSA has been regarded as α-synucleinopathy along with Parkinson disease (PD), dementia with Lewy bodies and pure autonomic failure (PAF). Quinn proposed the first set of diagnostic criteria and distinguished the motor subtypes MSA-P and MSA-C, although there was unintended overlap. Further, he allowed an abnormal external sphincter electromyogram (EMG) as diagnostic criterion, thereby creating practical difficulties [7]. For these reasons a consensus conference was convened in 1998 that proposed exclusively clinical guidelines for the diagnosis of MSA. Subdivision into MSA-P and MSA-C was recommended based on the predominant motor feature at presentation [8]. Based on improvements of early diagnosis by defining warning signs (red flags) and sensitive neuroimaging indices, the consensus guidelines were revised 10 years later [9]. A unified MSA rating scale (UMSARS) quantifying disease severity has been established and validated in the meantime by the European MSA Study Group (EMSA-SG) [10]. UMSARS has been applied in the EMSA natural study, confirming the rapid progression of autonomic failure, cerebellar ataxia and parkinsonism (G. K. Wenning *et al.*, unpublished data). Animal models have become available as preclinical testbeds for translational neuroprotection and neuroregeneration studies [11]. The first clinical trials have been conducted by two independent consortia using minocycline (EMSA-SG) [12] and riluzole (Neuroprotection and Natural History in Parkinson-Plus Syndromes [NNIPPS]) [13]. Other international networks have been established in the last few years including NAMSA (North American MSA Study Group) [14], JAMSAC (Japanese MSA Consortium) and CNMSA (Chinese MSA Study Group). Globalization of MSA research has led not only to the aforementioned trial activities but also to the first genetic breakthrough by indentifying variants in the α-synuclein gene and their association with increased disease risk in a large population of MSA patients [15]. In addition several pedigrees with monogenic MSA but yet unidentified loci have been reported [16].

Clinical findings

Clinically, cardinal features include autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination (Table 1.1). Two major motor presentations can be distinguished. In the western hemisphere

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Table 1.1. Clinical presentation of MSA according to the EMSA Registry.

437 patients (53% male; mean age at disease onset 58 years; mean disease duration 5.8 years; 68% MSA-P; 32% MSA-C)
Autonomic failure
• Urinary symptoms (83%)
– Urge incontinence (73%)
– Incomplete bladder emptying (48%)
– Erectile failure (84%)
• Orthostatic hypotension (75%; syncope 19%)
• Chronic constipation (33%)
Parkinsonism
• Bradykinesia and rigidity (93%)
• Postural instability (89%)
• Rest tremor (33%)
• Freezing of gait (38%)
Cerebellar ataxia
• Gait ataxia (86%)
• Limb ataxia (78%)
• Ataxic dysarthria (69%)
Pyramidal signs
• Babinski sign (28%)
• Generalized hyperreflexia (43%)
Neuropsychiatric features
• Depression (41%)
• Hallucinations (5.5%)[a]
• Dementia (4.5%)[a]
• Insomnia (19%)
• Daytime sleepiness (17%)
• Restless legs (10%)

Modified according to Koellensperger and Wenning [17].
[a] Patients were entered on the basis of expert opinion regardless of diagnostic criteria.

parkinsonian features predominate in 60% of patients (MSA-P subtype, Figure 1.1), cerebellar ataxia is the major motor feature in 40% of patients (MSA-C subtype) [17]. The reverse distribution is observed in the eastern hemisphere [18,19]. MSA-associated parkinsonism is dominated by progressive akinesia and rigidity, whereas tremor is less common than in PD. Postural stability is compromised early on; however, recurrent falls at disease onset are unusual in contrast to progressive supranuclear palsy. The cerebellar disorder of MSA is composed of gait ataxia, limb kinetic ataxia, and scanning dysarthria, as well as cerebellar oculomotor disturbances. Dysautonomia develops in virtually all patients with MSA [20]. Early impotence (erectile dysfunction) is virtually universal in men, and urinary incontinence or incomplete bladder emptying, often early in the course or as presenting symptoms, are frequent. Orthostatic hypotension is present in two-thirds of patients [17]. Progressive hypohidrosis is also prominent.

The clinical diagnosis of MSA rests largely on history and physical examination. The revised consensus criteria [9] specify three diagnostic categories of increasing certainty: possible, probable, and definite. Whereas a definite diagnosis requires neuropathological evidence of a neuronal multisystem degeneration (SND, OPCA, central autonomic degeneration) and abundant GCIs [21], the diagnosis of possible and probable MSA is based on the presence of clinical and imaging features (Tables 1.2–1.4). In addition, supportive features (warning signs or red flags) as well as nonsupportive features may be considered (Tables 1.5 and 1.6).

Natural history and progression

The disease affects men and women alike. It usually starts in the sixth decade and progresses relentlessly until death on average 9 years after disease onset [4,13,23]. There is a considerable variation of disease duration, with survival times of up to 15 years or more. Predictors of poor outcome include female sex, older age at onset, autonomic failure and rapid progression [24]. The motor variants of MSA are associated with similar survival [25], although disease progression is more rapid in MSA-P than in MSA-C patients [18]. Most MSA patients succumb to sudden death reflecting central cardiovascular or respiratory disturbances due to loss of serotonergic neurons in the ventrolateral medulla [26]. Other causes of death may include aspiration pneumonia or pulmonary embolism.

The recent natural history study by the EMSA-SG applied the unified MSA rating scale (UMSARS) [10] and confirmed rapid progression with an average increase of UMSARS I scores (reflecting activities of daily living) by 16.8% in the first 6 months compared with baseline. Further, UMSARS II (motor examination) scores increased by 26.1% and UMSARS IV (global disability) scores by 12.5% [27].

Investigations

The diagnosis of MSA rests on both history and neurological examination. Additional investigations may be performed according to the consensus criteria

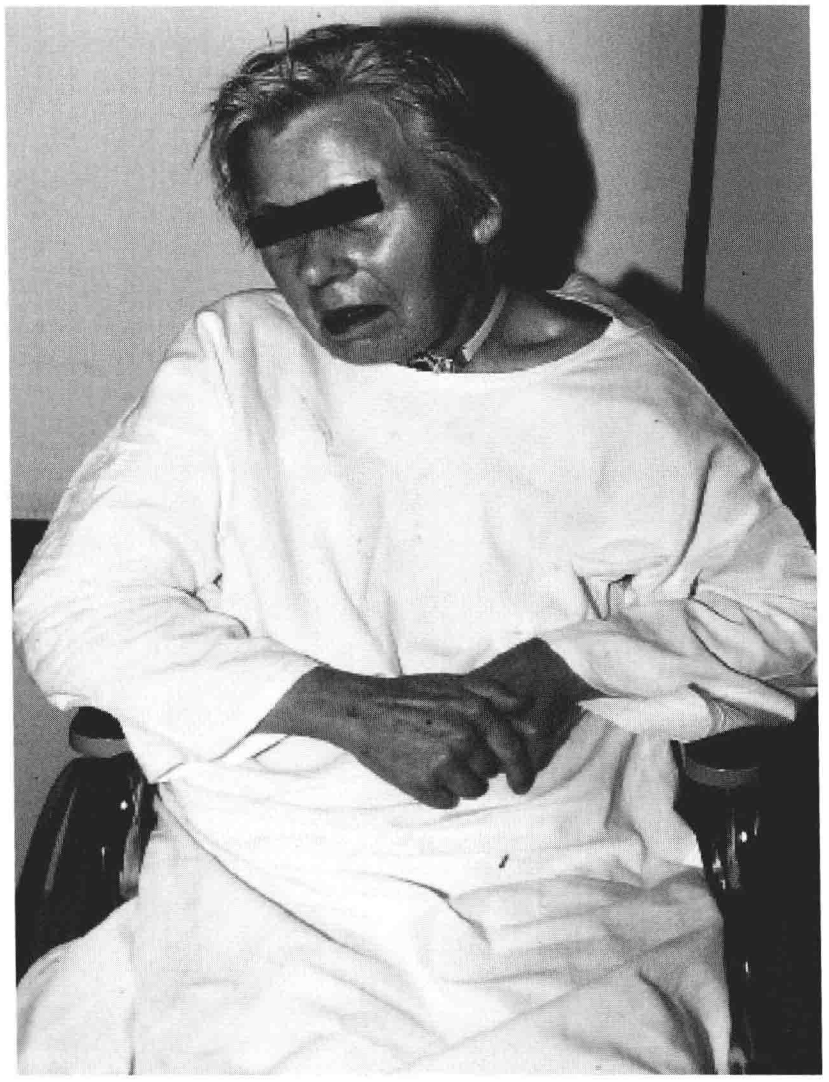

Figure 1.1. MSA-P patient with non-L-dopa-responsive akinetic-rigid parkinsonism and early development of the "wheelchair sign." In addition, the patient showed a disproportionate antecollis and a pronounced inspiratory stridor that caused respiratory failure leading to tracheostomy. (Reproduced from Wenning *et al.* [142] with kind permission of Springer Science+Business Media.)

(Table 1.7). These include cardiovascular autonomic function tests, external sphincter EMG and neuroimaging. However, previous studies have largely been conducted in patients with advanced MSA and therefore the diagnostic validity of additional testing in early MSA remains to be determined.

Pathology

A definite diagnosis of MSA requires neuropathological evidence of glial cytoplasmic inclusions (GCIs) in association with selective neurodegeneration (Figure 1.2) [21]. Specifically, there is neuronal loss and gliosis of the striatum, substantia nigra pars compacta (SNc), locus ceruleus, cerebellum, pontine nuclei, inferior olives, intermediolateral columns and Onuf's nucleus [28]. This neurodegenerative pattern is characterized by astrogliosis, microglial activation, microgliosis and myelin loss [29–32].

Multiple system atrophy is a unique oligodendrogliopathy [33] with widespread and abundant GCIs (Papp–Lantos bodies) that were first identified in 1989 by Gallyas silver impregnation [6,34]. GCIs contain filamentous α-synuclein [1,6,35–38] linking MSA with the spectrum of neuronal α-synucleinopathies such as PD, dementia with Lewy bodies and pure autonomic failure. GCIs are argyrophilic flame-shaped aggregates[39] that in addition to α-synuclein comprise other constituents, identified to date by either

Table 1.2. Consensus criteria for the diagnosis of probable MSA.

A sporadic, progressive, adult-onset (>30 years) disease characterized by:

- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 minutes of standing by at least 30 mmHg systolic or 15 mmHg diastolic and
- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Modified according to Gilman *et al.* [9] and reproduced from Wenning and Stefanova [22] (with kind permission of Springer Science+Business Media).

Table 1.3. Consensus criteria for the diagnosis of possible MSA.

A sporadic, progressive, adult-onset (>30 years) disease characterized by:

- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features shown in Table 1.4

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Table 1.4. Additional features of possible MSA.

Possible MSA-P or MSA-C

- Babinski sign with hyperreflexia
- Stridor

Possible MSA-P

- Rapidly progressive parkinsonism
- Poor response to levodopa
- Postural instability within 3 years of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 years of motor onset
- Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum

Possible MSA-C

- Parkinsonism (bradykinesia and rigidity)
- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
- Hypometabolism on FDG-PET in putamen
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

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immunohistochemistry or mass spectrometry. These include for example ubiquitin, tubulin and p25α (Table 1.8) [29,33,40,41].

Localization of GCIs is widespread and their appearance has been correlated with severe neuronal loss as well as disease duration and severity [42,43]. The cellular inclusion pathology is not restricted to GCIs. Neuronal cytoplasmic inclusions (NCIs) and neuronal nuclear inclusions (NNIs) have also been observed, mainly restricted to the putamen, substantia nigra, inferior olivary nucleus, motor cortex, dentate gyrus and pontine nuclei [44–52].

Table 1.5. Supportive features (red flags) for a diagnosis of MSA.

- Orofacial dystonia
- Disproportionate antecollis
- Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)
- Contractures of hands or feet
- Inspiratory sighs
- Severe dysphonia
- Severe dysarthria
- New or increased snoring
- Cold hands and feet
- Pathological laughter or crying
- Jerky, myoclonic postural/action tremor

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Table 1.6. Nonsupportive features for a diagnosis of MSA.

- Classic pill-rolling tremor
- Clinically significant neuropathy
- Hallucinations not induced by drugs
- Onset age after 75 years
- Family history of ataxia or parkinsonism
- Dementia on (DSM-IV)
- White matter lesions suggesting multiple sclerosis
- Pathological laughter or crying
- Jerky, myoclonic postural/action tremor

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The factors triggering and maintaining progressive α-synuclein accumulation in oligodendrocytes are still unknown, but the finding of oligodendroglial p25α accumulation predating GCI formation as well as alterations of myelin basic protein support a primary oligodendrogliopathy [33,53–58].

Etiopathogenesis

Environmental factors

The underlying etiopathogenesis of MSA is still unclear, but complex interactions of genetic and environmental factors, similar to other sporadic neurodegenerative diseases, appear to be likely [59]. In a few controlled studies, an increased risk of developing MSA by occupational and daily habits, such as exposure to solvents, additives, plastic monomers, metals and various other toxins [8,60,61], as well as history of farming [59,61] has been observed. A recent study, however, questioned some of the associations [62].

In general, convincing findings from environmental studies, are hard to obtain to owing limiting factors such as recall (over-reporting of exposure) and selection bias (patients with severe diseases are less able to participate) [63]. Hence the role of environmental factors is far from clear.

Genetic factors

MSA seems to occur sporadically and, compared with PD, few families have been reported with a family history of MSA [64,65]. Lately, an autosomal recessive inheritance pattern of MSA was reported in Japan [16,66]. Furthermore, some studies suggest that MSA-like features are in close relation with various forms of spinocerebellar ataxia [67–71].

Several investigators addressed potential abnormalities of the α-synuclein gene in MSA due to its postulated etiologic role [6,33,36]. Early studies (including sequencing of *SNCA* coding sequence, gene dosage measurements, microsatellite testing and haplotype studies) had failed to identify significant associations with the α-synuclein gene owing to insufficient sample size [72–75]. A recent genome-wide association study by the EMSA-SG and associated consortia identified a number of single nucleotide polymorphisms (SNPs) within the α-synuclein gene that were associated with increased MSA disease risk [15]. These findings were recently confirmed in an independent patient cohort [76]; however, the genetic background of the control population appears to be of importance when interpreting disease risk [77]. Further, polymorphisms of genes involved in inflammatory processes, such as interleukin-1α, interleukin-1β, interleukin-8, intercellular adhesion molecule-1 and tumor necrosis factor showed elevated odds ratios in MSA cohorts compared with controls [78–82]. Polymorphism of genes involved in oxidative stress as well as the alpha-1 -antichymotrypsin AA genotype (ACT-AA) were also related to MSA risk [83]. In contrast, other genes coding for apolipoprotein E, dopamine β-hydroxlyase, ubiquitin C terminal hydrolase-1, fragile x mental retardation 1 and leucine-rich kinase 2 showed no significant association [74].

Table 1.7. Additional investigations in MSA.

Investigation	Typical results
Cardiovascular autonomic function tests	Orthostatic hypotension (≥20/10 mmHg systolic/diastolic blood pressure drop) Impaired reflex tachycardia Impaired heart rate variability Impaired Valsalva maneuver Impaired rise of plasma noradrenaline upon standing
Arginine/clonidine challenge test	Impaired release of growth hormone (controversial)
Thermoregulatory sweat test (TST), quantitative sudomotor axon reflex test (QSART)	Sudomotor dysfunction (an-/hypohidrosis) due to pre- and postganglionic sympathetic failure
Sympathetic skin response	Abnormal or absent
CSF	Increased neurofilament (light and heavy chain) level
External anal sphincter EMG	Denervation (nonspecific)
Transcranial sonography	Lentiform hyperechogenicity and nigral normoechogenicity
CCT	Unhelpful
MRI (1.5 tesla)	Basal ganglia abnormalities (putaminal atrophy/ hyperintense putaminal rim/ putaminal hypointensity, infratentorial signal change – hot cross bun sign), cerebellar and/or brain stem atrophy
MRI (DWI)	Increased diffusivity of putamen (posterior > anterior), rostral pons and middle cerebellar peduncle
MR volumetry	Regional volume loss (putamen in MSA-P, MCP, brainstem and cerebellum in MSA-C)
FP-CIT SPECT	Reduced striatal dopamine transporter binding
IBZM SPECT	Reduced striatal dopamine D2 receptor binding
F-Dopa-PET	Reduced striatal F-dopa uptake
C-Raclopride-PET	Reduced striatal dopamine D2 receptor binding
F-PK11195-PET	Microglial activation in basal ganglia and brainstem areas
FDG-PET	Reduced striatal, frontal, and infratentorial metabolism
MIBG scintigraphy	Preserved myocardial MIBG uptake

Animal models

The role of oligodendroglial α-synucleinopathy as a trigger of MSA-like neurodegeneration has been investigated in transgenic mice with targeted overexpression of human α-synuclein under the control of specific oligodendroglial promoters. Insolubility and hyperphosphorylation of α-synuclein reproduced the main feature of human GCI pathology in transgenic mice and further induced neuronal loss involving (i) axonal α-synuclein aggregation and axonal degeneration [84], (ii) mitochondrial dysfunction [42], (iii) microgliosis [85], or (iv) environmental oxidative stress [86,87]. The transgenic models with α-synuclein overexpression are useful experimental tools to study basic mechanisms related to GCI-pathology in vivo; however, they also have well-recognized limitations such as not being able to replicate complete MSA-like degeneration and no documented MSA-like change in CNS neurotransmitter expression.

Management

Therapies

Currently, there is no effective neuroprotective therapy in MSA. Symptomatic treatment is largely restricted to parkinsonism and dysautonomia. Other features such as cerebellar ataxia appear to be unresponsive to drug treatment.