An update on the cerebellar subtype of multiple system atrophy

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Abstract

Multiple system atrophy is a rare and fatal neurodegenerative disorder characterized by progressive autonomic failure, ataxia and parkinsonism in any combination. The clinical manifestations reflect central autonomic and striatonigral degeneration as well as olivopontocerebellar atrophy. Glial cytoplasmic inclusions, composed of α-synuclein and other proteins are considered the cellular hallmark lesion. The cerebellar variant of MSA (MSA-C) denotes a distinctive motor subtype characterized by progressive adult onset sporadic gait ataxia, scanning dysarthria, limb ataxia and cerebellar oculomotor dysfunction. In addition, there is autonomic failure and variable degrees of parkinsonism. A range of other disorders may present with MSA-C like features and therefore the differential diagnosis of MSA-C is not always straightforward. Here we review key aspects of MSA-C including pathology, pathogenesis, diagnosis, clinical features and treatment, paying special attention to differential diagnosis in late onset sporadic cerebellar ataxias.

Keywords: Multiple system atrophy, Cerebellar type, Idiopathic late onset cerebellar ataxia, Sporadic adult onset ataxia

Introduction

Multiple system atrophy (MSA) is a rare, sporadic, progressive, neurodegenerative disorder combining features of parkinsonism, autonomic dysfunction and cerebellar and pyramidal signs. MSA can be further classified in parkinsonian-type MSA (MSA-P) and cerebellar-type MSA (MSA-C) according to the predominant motor symptoms at evaluation.

MSA has a prevalence of 1.9-4.9 cases per 100000 [1,2] and an incidence of 0.6/100000, raising up to 3/100000 in people older than 50 years [3].

MSA-P is the more common variant in Europe and in USA, accounting for about 65% of all cases [4-6]. In the Japanese population MSA-C is present in 83.8% of MSA patients at first examination and in 48.6% of patients at last follow-up [7]. This difference could be caused by, not yet fully understood, genetic predisposition and environmental influences in the pathogenesis of the disease. Median survival ranges from 6 years to about 9 years [6,8,9].

Here, we aim to provide an update on the pathology, pathogenesis, diagnosis, clinical presentation and latest therapeutic development in MSA-C. We searched the following terms on PubMed: “multiple system atrophy”, “idiopathic late onset cerebellar ataxia”, “sporadic adult onset ataxia”. In addition, reference lists in review papers were systematically checked for relevant references. Only papers in English were reviewed.

Review

Pathology

Twenty years ago Papp and coworkers identified, for the first time, the argyrophilic filamentous aggregates localized in the cytoplasm of oligodendrocytes that were common to all MSA variants. These inclusion bodies were subsequently termed glial cytoplasmic inclusions (GCIs) or Papp-Lantos bodies [10]. GCIs are typically associated with gliosis and neuronal loss in the basal ganglia, cerebellum, pons, inferior olivary nucleus, and spinal cord. Frequently a striatonigral (SND) or olivopontocerebellar (OPCA) pattern of atrophy can be defined. Patients can present either a balanced damage in both regions or a predominant involvement of one system over the other. In both cases, the pathological alteration determines the clinical phenotype, i.e. clinically diagnosed MSA-C often reflects underlying OPCA [11-14]. In MSA pathological alterations are not limited to OPCA and SND but many
other brain regions can be involved. Degeneration of several autonomic nuclei in the brainstem and spinal cord is traditionally believed to account for autonomic failure in MSA [15-17]. However, a growing body of evidence suggests that post-ganglionic denervation also occurs in MSA patients, and may be involved in the pathogenesis of dysautonomia [18-21]. Accordingly, the sudomotor nerve density in the sweat glands has been found to be reduced in patients with MSA as compared to healthy controls. Interestingly, peripheral nerve degeneration has been found in the early course of the disease, and may, therefore, be independent of degeneration of autonomic CNS nuclei [21].

In the late 1990’s, α-synuclein was identified as the main component of GCIs [22-25]. Widespread GCIs cannot be found in other diseases and are always present in patients with MSA, regardless of the clinical phenotype. Their assessment is considered as the only reliable criteria for the diagnosis of definitive MSA [26,27]. Additionally, neuronal cytoplasmic inclusions (NCIs) and neuronal nuclear inclusions (NNIs) can be found in MSA as well, however, they are only of limited diagnostic value [28].

Of note, however, α-synuclein is not the only component of GCIs. Ubiquitin, tau, p25α, members of the heat shock protein family, dopamine and c-AMP-regulated phosphoprotein-32 (DARP-32), and many other proteins have been detected in different proportion in GCIs [17]. Of interest, p25α, a normal constituent of myelin sheets in healthy neurons, seems to have a facilitatory effect on GCIs formation, and its dislocation from the axons to the soma of oligodendrocytes [29] might therefore have a causative role in α-synuclein aggregation [30].

Pathogenesis

Aberrant protein aggregation and dislocation can enhance neuronal demise [31,32] by disrupting the cytoskeleton [33]. While NNIs and NCIs directly damage neurons, GCIs primarily promote oligodendrocytes death [34-36], thereby causing secondary neurodegeneration. This assumption is also supported by evidence that GCI density correlates with disease duration and neuronal loss [13].

The most accredited theory linking oligodendrocyte damage with neuronal death focuses on disruption of the crosstalk between these cells. Oligodendroglial dysfunction results into an abnormal synthesis and release of trophic factors and other signal molecules, thereby triggering neuronal apoptosis [13,37].

Dysfunction of the mitochondrial respiratory chain may also contribute to the pathophysiology of MSA, as suggested by the evidence that variants in the COQ2 gene that reduce the function of parahydroxybenzoate-polyprenyltransferase (an enzyme necessary for the biosynthesis of coenzyme Q10) are associated with an increased risk of developing MSA [38]. Mitochondrial dysfunction leads to an excessive production of reactive oxygen species (ROS) [39,40], which have been implicated in the pathogenesis of MSA-associated neuronal damage [41,42]. ROS species are also generated by activated microglia, together with other damaging factors, such as nitrogen species and cytokines [43-45] (Figure 1) [17]. Microglial activation can be partially explained by an aberrant expression of Toll-like receptors (TLRs) in brain regions involved in OPCA and SND [46]. An imbalance of TLR signaling could enhance MSA-related brain injury by promoting pro-inflammatory signals [47,48].

In spite of the recent advances in the understanding of the pathogenesis of MSA, many questions remain unanswered. The influence of environmental and genetic factors remain unresolved in the western hemisphere. Although early reports suggested an association between MSA and agricultural work, the role of toxic substances could not be unequivocally proven [33]. Genetic inheritance is uncommon and there are few reports of familiar MSA in the literature [49-51]; however, the genetic background is important and single nucleotide polymorphisms (SNPs) of the genes encoding α-synuclein [52-54], the prion protein [55], and loss of function mutations of the phenylbenzoate-polyprenyltransferase were shown to be associated with an increased risk of MSA [38].

The origin of the α-synuclein found in GCIs is still unknown. Miller and coworkers failed to detect the expression of the gene coding for α-synuclein (the SNCA gene) in oligodendrocytes using double-labeling in situ hybridization technique [56]. Recently, however, α-synuclein mRNA could be measured in oligodendrocytes by laser-capture microdissection technique. mRNA levels in oligodendrocytes did not differ between MSA patients and healthy controls, although there was a trend to an increase in MSA patients [57]. Proteasomal and autophagic degradation of α-synuclein has also been found to be impaired in affected oligodendrocytes [17,56,58].

An increased uptake of α-synuclein from the extracellular environment, particularly from the cerebrospinal fluid (CSF) [59], may also contribute to GCI formation and propagation [60,61]. Reyes et al. (2014) [61] have shown that oligodendrocytes grafted in the striatum of rats overexpressing human α-synuclein, take-up the protein from surrounding axon terminals. This evidence suggests a prion-like propagation of α-synuclein in MSA, similarly to what hypothesized for Parkinson’s disease [62,63].

Clinical features

MSA-C patients develop the first motor or autonomic symptoms at the mean age of 56 years [64,65]. Postmortem confirmed MSA-C has never been reported in patients younger than 30 years. If symptoms appear for the first
time in patients older than 75 years, the diagnosis of MSA should be questioned [27]. Motor symptoms in MSA-C are often preceded by autonomic and other non-motor features [15,64]. Erectile dysfunction and urinary problems, such as incontinence and urinary retention, are frequently the first manifestation of autonomic failure in MSA-C [15,64,66,67]. Postural faintness tends to occur later [15,64,66,68]. Other symptoms of autonomic failure in MSA-C include reduced sweating and constipation. Recently, Iodice and colleagues (2012) [69] reported that
the most common cerebellar feature at motor presentation is ataxic gait, followed by dysarthria, limb ataxia and gazed-evoked nystagmus. Although nystagmus is uncommon, other oculomotor abnormalities, such as jerky pursuit, square wave jerks, and dysmetric saccades are frequently observed in the early course of the disease [27]. Hyperreflexia and positive Babinski sign are classical manifestations of pyramidal tract degeneration and are frequently assessed in MSA-C patients.

Parkinsonism occurs about 5 years after the onset of MSA-C [70] and is usually characterized by a akinetic-rigid syndrome. Parkinsonian symptoms in MSA-C patients may respond to levodopa (L-DOPA) in up to 51% of cases, however, the effect is often transient and some patients also develop L-DOPA-induced dyskinesias [65].

Craniofacial dystonia is a common cause of postural aberrations such as camptocormia and Pisa syndrome. Dystonic involvement of face, hands and feet is also possible. Laryngeal abductor palsy resulting in stridor, can also be present. It commonly appears late in the disease course and is a possible cause of sudden death [71].

Ataxia, parkinsonism and postural impairment all contribute to gait instability, occurring early after the disease onset [64,72].

Microcirculatory abnormalities are common in MSA-C patients and are responsible for the so called “cold hand sign” [73-75].

Tison and colleagues [76] reported that about 30% of patients with MSA-C experience pain. The most common form is musculoskeletal pain, followed by sensory and dystonic pain.

Almost all patients with MSA develop REM sleep behavior disorder (RBD), a condition that is characterized by violent movements and nightmares during REM sleep [77]. In a small series of 13 MSA-C patients, RBD was found to precede waking motor symptoms in 3 patients and was present at diagnosis in about 50% of cases [78]. Curiously, RBDs commonly improve along with disease progression [75]. Excessive daytime sleepiness has been reported in about 25% of MSA-C patients, and might stem from low quality of sleep and/or dysfunction in neuronal pathways of arousal [79,80].

Many authors described cognitive impairment, involving executive functions and verbal learning in MSA-C [81-86]. These deficits are probably due to frontal atrophy [82,84] and white matter networks disruption [81,87].

Finally, psychiatric syndromes such as depression [86], anxiety [85] and pathological laughing and crying [88], affect MSA-C patients more frequently than the general population.

Diagnosis
According to current consensus diagnostic criteria [27], three different categories of increasing diagnostic certainty were defined. A definite diagnosis of MSA requires post-mortem examination. Probable MSA-C is defined by the presence of cerebellar ataxia and either limb ataxia, cerebellar dysarthria or cerebellar oculomotor dysfunction, together with autonomic dysfunction in the form of urinary incontinence and erectile dysfunction or severe orthostatic hypotension defined as a drop in systolic or diastolic blood pressure of 30 mmHg and 15 mmHg within 3 minutes after standing, respectively.

If only a mild autonomic dysfunction is found, possible MSA-C can be diagnosed taking into account pyramidal signs, parkinsonism, and imaging findings. T2-weighted MRI can reveal the so called “hot cross bun sign”, a cruciform hyperintensity in the ventral part of pons. This is one of the most distinctive although not pathognomonic imaging findings in MSA-C and has been reported in up to 81.4% of patients [64]. It is due to demyelination and fibrosis of transverse fibers in pons and it can be assessed also in other pathologies involving the pons, such as different types of SCAs, particularly SCA 2 [89]. Middle cerebellar peduncle hypointensity, lateral putaminal rim hyperintensity and putaminal hypointensity, are also considered in the diagnosis of possible MSA-C.

Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) are MRI techniques that are considered still investigational in the latest MSA guidelines [27]. They can detect early alterations in the infratentorial region of MSA patients [90,91] and show a higher sensitivity compared to T2-weighted MRI for the “hot cross bun sign” [92]. Because of its high sensitivity, DTI might be helpful for the differential diagnosis in patients with cerebellar symptoms even in the earlier stages of MSA-C, (see below). DWI and DTI have also been proposed as possible markers for the progression of the disease [93].

Striatal dopaminergic denervation or glucose hypometabolism assessed with SPECT or PET, respectively, in the presence of cerebellar symptoms suggests the diagnosis of MSA-C rather than other forms of late onset ataxia (Table 1).

Warning symptoms, also called “red flags”, may facilitate the diagnosis of MSA (Table 2) [94]. Disease progression can be quantified using the Unified MSA Rating Scale (UMSARS) [95]. It involves assessment of the activities of daily living (ADL) (UMSARS I), the motor function (UMSARS II), a simple standing test to determine the presence and magnitude of OH (UMSARS III) and a global disability scale (UMSARS IV).

Differential diagnosis
MSA-like cerebellar symptoms, are shared by many other primary and secondary cerebellar disorders. Secondary ataxia can be caused by toxins, infections, tumors, vitamin deficiency and several other pathologies. Primary diseases
can be caused by mutations (spinocerebellar ataxias (SCAs) and Fragile-X related tremor and ataxia syndrome (FXTAS)), or remain idiopathic.

Alcohol is a common cause of ataxia, with the percentage of alcoholics developing ataxia ranging from 11% to 27% [96,97]. The possible relation between alcohol intake and cerebellar symptoms should be carefully assessed for a correct diagnosis. An improvement of symptoms after alcohol withdrawal is strongly indicative for alcoholic ataxia [98,99].

Table 2 Red flags for MSA, reproduced with the courtesy of Wiley and Sons [85]

| Red flag                      | Definition                                                                 |
|-------------------------------|-----------------------------------------------------------------------------|
| Early instability with recurrent falls | within 3 years of disease onset                                              |
| Rapid progression              | "wheelchair sign": dependent < 10 years from disease onset                  |
| Orofacial dystonia             | based on clinical judgment                                                  |
| Camptocormia                  | prolonged episodes of forward trunk flexion                                 |
| Pisa syndrome                 | prolonged episodes of lateral trunk flexion                                 |
| Disproportionate antecollis   | severe neck flexion, minor flexion elsewhere                                |
| Contractures of hands or feet | excluding Dupuytren’s or contracture due to other known cause               |
| Jerky tremor                  | irregular postural or action tremor of the hands and/or fingers with definite myoclonus |
| Diurnal inspiratory stridor   | based on clinical judgment                                                  |
| Nocturnal inspiratory stridor | based on clinical judgment                                                  |
| Inspiratory sighs             | involuntary deep inspiratory sighs/gasps                                    |
| Severe dysphonia              | based on clinical judgment                                                  |
| Severe dysarthria             | based on clinical judgment                                                  |
| Severe dysphagia              | based on clinical judgment                                                  |
| REM sleep behavior disorder   | intermittent loss of muscle atonia and appearance of elaborate motor activity (striking out with arms in sleep often with talking/shouting) associated with dream mentation |
| Sleep apnoea                  | prolonged arrests of breathing                                              |
| Excessive snoring             | increase from premorbid level, or newly arising                             |
| Cold hands/feet               | new development of coldness and color change – purple/blue – of extremities, with blanching on pressure and poor circulatory return |
| Raynaud’s phenomenon          | new emergence of painful "white fingers"                                   |
| Emotional incontinence – crying | Inappropriate crying without sadness                                       |
| Emotional incontinence – laughing | Inappropriate laughing without mirth                                      |
| Past history of documented hypertension | based on clinical judgment                                                  |
Several drugs can cause cerebellar damage [98,100-103]. It is, therefore, important to evaluate all medications taken by the patients, keeping in mind their possible adverse effects.

An important cause of late onset ataxia is a paraneoplastic syndrome. Small cell lung cancer, ovarian cancer, breast cancer, and Hodgkin’s lymphoma are most usually associated with cerebellar injury [98]. This damage is commonly related with the production of circulating antineural antibodies directed against antigens expressed by neoplastic cells [104,105]. Peripheral blood testing, combined with the assessment of rapid progressive ataxia and systemic symptoms such as fever, malaise and anorexia in the absence of cerebellar abnormalities at MRI at the onset of motor symptoms, usually leads to the diagnosis of paraneoplastic cerebellar ataxia within 6 months [104]. Vitamin deficiency, superficial siderosis and infections can also cause ataxia (reviewed by Klockgether, 2010) [98].

Finally, ataxia can also be associated with autoimmune disorders. Anti-glutamate decarboxylase (GAD) antibodies positive ataxia is more frequent in diabetic patients [106] and in patients with polyglandular autoimmune disorder [107]. Gluten ataxia is a sporadic form of ataxia developing after chronic ingestion of gluten, with or without association with coeliac disease. Gluten ataxia is diagnosed if antigliadin antibodies are found in ataxic patients in the absence of other potential causes [108,109]. Anti-transglutaminase (TG) autoantibodies can also be found in patients with gluten ataxia. In particular, antibodies directed against TG 6, the most abundant TG isofrom in the CNS, are specifically associated with gluten ataxia [110].

The collection of an accurate family history is important, but not always sufficient, to rule out genetic forms of ataxia. Late onset autosomal dominant SCAs, such as SCA6 [111,112], may be difficult to diagnose if the affected relatives died before developing the illness. In a study, genetic analysis was performed in patients with negative family history who developed ataxia when they were at least 25 years old. SCA6 was the predominant genetic form, but also mutations associated with SCA2 and SCA3 were found in few patients [113]. It is worth noting that in Asians and Africans SCA2 and SCA3 mutations cause L-DOPA-responsive parkinsonism [114,115].

A premutation of the FMR1 gene causes a late onset form of ataxia called FXTAS. This disease is characterized by cerebellar ataxia, postural and intentional tremor, dementia, neuropathy, and several psychiatric manifestations [116]. A large investigation by Kamm and coworkers (2005) [117] showed that FMR1 premutation-associated ataxia is distinct from MSA-C. Nevertheless, the possible diagnosis of FXTAS has to be considered especially in the presence of slow disease progression, neuropathy and dementia. These clinical features are common among patients with FXTAS, and their assessment may help to differentiate the two disorders.

Most of the above conditions can be diagnosed with an accurate history. It is more difficult to differentiate MSA-C with sporadic adult onset ataxia (SAOA). SAOA, also known as idiopathic late onset cerebellar ataxia (ILOCA), is a rare form of ataxia, with a prevalence of about 8.4 per 100000 [118]. The age at onset for both MSA-C and SAOA is around 50 years [118]. However, the mean survival time is much longer in SAOA than in MSA-C. SAOA is not only associated with a better prognosis but also with a delayed deterioration in ADL. Patients with MSA require a wheelchair within 5 years of onset [64]; in contrast, about half of patients with SAOA can still walk unaided after 12 years [113,119].

A reliable differential diagnosis between SAOA and MSA-C can usually be performed years after the onset. Within 5 years from the diagnosis, about ¼ of patients with idiopathic late onset cerebellar ataxia are diagnosed as affected by MSA-C [113,120,121]. This can be easily explained considering that the presence of autonomic and motor signs is mandatory for the diagnosis of MSA-C [27] and that autonomic dysfunction becomes manifest only 2–2.5 years after the first cerebellar signs [64,70]. Initial clinical presentation do not help much in the differential diagnosis. Although nystagmus, gaze paralysis, decreased or absent ankle reflex are more common in SOAO [121,122], many motor and non-motor symptoms [123], RBD [75,122] and erectile dysfunction [68,122], are shared by MSA-C and SAOA.

The differential diagnosis between SAOA and MSA-C has been the subject of several studies. However, the large majority of these studies compared fully developed MSA and SAOA, whereas the differential diagnosis is particularly difficult in the early phase of the disease. T2-weighted MRI is used for the diagnosis of MSA [27] and has good specificity in differentiating fully developed MSA-C from SAOA [124]. Other MRI based techniques were used for the differential diagnosis between MSA-C and other ataxias, with interesting results. Proton MR spectroscopy imaging distinguished MSA-C from SCA2 on the basis of different levels of lactate in cerebellum [125]. DTI yielded a different fractional anisotropy in MSA-C and many other types of ataxia, but not SAOA [126]. A more valuable diagnostic tool is the measurement of cerebral blood flow in the pons by Fine-STR, which is lower in MSA-C than in SAOA [127].

In MSA-C there is loss of motor units innervating the external anal and urethral sphincter muscles reflecting degeneration of Onuf’s nucleus. These changes together with detrusor hyperreflexia account for early neurogenic bladder incontinence in MSA-C and they may help differentiate MSA-C from other sporadic late onset cerebellar
ataxias in the first 5 years after the onset of the disease [128]. Sphincter denervation can be evaluated by means of anal sphincter electromyography (EMG) and urethral sphincter EMG [128-132]. The former is better tolerated by patients [129]. However, anal sphincter EMG is not highly sensitive in the early course of the disease, and it was positive only in 52% of patients with disease duration shorter than 1 year [130].

Measurements of proteins and monoamine metabolites in the cerebrospinal fluid (CSF) are particularly valuable in the diagnosis of chronic neurodegenerative disorders. Putative CSF biomarkers include neurofilament light chain (NFL), phosphorylated neurofilament heavy chain, α-synuclein, β-amyloid, tau, the noradrenaline metabolite, 3-methoxy-4-hydroxyphenylethylenglycol (MHPG), and the dopamine metabolites, dihydroxyphenylacetic and homovanillic acids [58,133-136]. Abdo et al. (2006) [137] have found that a combined measurement of NFL, MHPG and tau has 100% specificity in differentiating between MSA and SAOA. Interestingly, the CSF obtained from MSA patients promotes aggregation of α-synuclein in a greater extent than the CSF obtained from SCAs patients [138].

For the diagnosis of MSA-C, EMG and CSF analysis are generally not recommended [27], because they are not helpful in full blown cases and have not been jet validated in early cases.

**Treatment**

Currently, the only treatments available for MSA-C are symptomatic. There are no approved drugs that can influence the disease course. The management of all possible manifestations of MSA is described in detail elsewhere [139-141]. Here, we will offer a brief description of the main therapeutic options that are currently available and will focus on new drugs under development.

**Symptomatic treatment**

Parkinsonism associated with MSA-C is treated with L-DOPA. Only half of patients with MSA-C respond to L-DOPA and dyskinesias, usually facial, are a common side effect [65]. When starting L-DOPA, a responsiveness test should be made with escalating doses in the first 3 months (up to a daily dose of 1000 mg if needed and tolerated) [142].

Currently, there is no treatment for cerebellar ataxia. The hypothesis of a possible effect of anticholinergic drugs is supported by the evidence that nicotine, which stimulates nicotinic cholinergic receptors in the CNS, can cause a reversible worsening of ataxic symptoms [10,143].

Urinary problems could be managed with drugs, at least at the beginning of the disease. The antimuscarinic drug, oxybutinin, reduces detrusor hyperreflexia and sphincter-detrusor dyssynergia, with positive effects on urgency and frequency [128,144]. Urinary retention is treated with α1-adrenergic antagonists, such as prazosin and moxysylate. All these drugs have important adverse effects that could limit their use. If postvoid residual volume exceeds 150 ml, although potentially difficult for ataxic patients, clean intermittent self-catheterization is indicated [144]. Many patients will eventually require a suprapubic catheter.

Orthostatic hypotension can be managed with non-pharmacological strategies. Adequate hydration of the patient has to be guaranteed [145]. Moreover, the patients should avoid large meals and increase sodium intake. Sitting or lying if feeling dizzy is recommended; if this is not possible, crossing legs, contracting thighs, and bending over can be helpful [146]. Abdominal and leg elastic garments are also effective in reducing orthostatic hypotension. Head-up tilt while sleeping reduces cerebral hyperventilation and increases circulatory volume within 1 week [140].

If these non-pharmacological measures fail, medical treatment is needed. Fludrocortisone is a potent agonist of mineralcorticoid receptors and increases blood pressure by enhancing sodium reuptake in the kidney. Alternatively, patients may be treated with the α1 adrenergic agonist, midodrine, or with the recently FDA approved adrenergic prodrug, droxidopa [147]. Finally, the vasopressin analogue, desmopressin, reduces nocturnal polyuria and morning hypotension [148].

Patients with postprandial hypotension may gain benefit by treatment with somatostatin analogues [141], which likely act by inhibiting the release of vasoactive gastrointestinal peptides [149].

Constipation is managed with high-fiber diet and, if necessary, macrogol-water solution.

Physiotherapy, speech therapy and occupational therapy may help patients coping with their disease [141].

**New treatments**

In the last years, many drugs have been tested as potential disease modifiers in MSA in general and MSA-C in particular. A growing body of evidence suggested efficacy in transgenic MSA mouse models [17]. However, growth hormone (GH) [150], the antiglutamatergic drug, riluzole [151], minocycline [152], rifampicin [153], and lithium [154] all failed to slow or halt disease progression in humans. A common feature of clinical trials with all these drugs, was to include patients in advanced stages, with fewer chances of gaining benefit by putative neuroprotective agents.

A Korean publication [155] reported beneficial effects of autologous bone marrow derived mesenchymal stem cells (MSC) in MSA patients, however these results have not been replicated so far and therefore remain experimentally until further confirmation studies are completed.
Finally, some interesting results were obtained by intravenous infusion of immunoglobulins, which are known to exert anti-inflammatory activity [156]. Seven MSA patients have been treated for 6 months and showed an improvement in UMSARS I and UMSARS II subscales, whereas UMSARS III and UMSARS IV remained unchanged [157]. This study was carried out on a small number of patients, without a control group. However, bearing in mind that a large deterioration in UMSARS is usually seen in one year [158], results are promising. In addition, α-synuclein lowering strategies have shown efficacy in preclinical synucleinopathy models, thus raising the possibility that these strategies may ultimately arrest disease progression in MSA [159].

Conclusions

Further advances in the diagnosis and treatment of MSA will go hand in hand. Novel neuroprotective strategies will be tested with the aid of novel diagnostic tools that allows an earlier start of the treatment.

Many ancillary exams with possible diagnostic value, such as MRI, anal sphincter EMG, CSF analysis and GH testing have been evaluated in MSA compared to other diseases. In our opinion, it becomes necessary to apply these diagnostic tools in patients with idiopathic cerebellar ataxia [113,120,121]. Hopefully, this new techniques will facilitate a differential diagnosis between MSA-C and SAOA at earlier time points. Clearly much is changed and many steps forward have been taken since Quinn portrayed MSA as a beast, in 1989 [160].

Abbreviations

ADL: Activities of daily living; CSF: Cerebrospinal fluid; DARPP-32: Dopamine and c-AMP-regulated phosphoprotein-32; DWI: Diffusion weighted imaging; DTI: Diffusion tensor imaging; EMG: Electromyography; FMR1: Fragile-X mental retardation 1; FXTAS: Fragile X related tremor and ataxia syndrome; GCs: Gliath cytoplasmic inclusions; GH: Growth hormone; ILOCA: Idiopathic late onset cerebellar ataxia; L-DOPA: Levodopa; MHPG: 3-methoxy-4-hydroxyphenylethylenglycol; MSA: Multiple system atrophy; MSA-C: Cerebellar type MSA; MSA-P: Parkinsonian type MSA; MSC: Mesenchymal stem cells; NCoTs: Neuronal cytoplasmic inclusions; NFL: Neurofilament light chain; NNI: Neuronal nuclear inclusions; OPCa: Olivopontocerebellar atrophy; RBD: REM sleep behavior disorders; SAOA: Sporadic adult onset ataxia; SCAs: Spinocerebellar ataxias; SNCs: Single nucleotide polymorphisms; TG: Transglutaminase; TLRs: Toll-like receptors; UMSARS: Unified MSA Rating Scale.

Competing interest

We have no competing interests.

Authors’ contributions

LC defined the search criteria, undertook the literature search, and the analysis and screening of papers, and wrote the paper. FK made critical revisions. FN helped writing the manuscript. GW defined the search criteria, and made the final revisions. All authors have seen and approved the final version.

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References

1. Schrag A, Ben-Shlomo Y, Quinn NP: Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 1999, 354:1771–5.
2. Wenning GK, Colosimo C, Geser F, Poewe W: Multiple system atrophy. Lancet Neurol 2004, 3:93–103.
3. Bower JH, Maraganore DM, Middick SK, Rocca WA: incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota. 1976 to 1990. Neurology 1997, 49:1284–8.
4. Geser F, Seppi K, Stampfler-Kountchev M, Kollensperger M, Diem A, Ntayiabata JP, Ostergaard K, Dupont E, Tardone A, Tolsa E, Abele M, Dodel R, Klockgether T, Ghorayeb I, Yekiley F, Tison F, Daniels C, Cooper R, Deuschl G, Coeho M, Fereira J, Rosa MM, Sampaio C, Boiz M, Schrag A, Hooker J, Kim H, Scarpelli T, Mathias CJ, Fowler C, et al: The European Multiple System Atrophy-Study Group (EMSA- SG). J Neurol Neurosurg Psychiatry 2005, 75:1267–76.
5. Kollensperger M, Geser F, Ntayiabata JP, Boesch S, Seppi K, Ostergaard K, Dupont E, Tardone A, Tolsa E, Abele M, Klockgether T, Yekiley F, Tison F, Daniels C, Deuschl G, Coeho M, Sampaio C, Boiz M, Quinn N, Schrag A, Mathias CJ, Fowler C, Nilsen CF, Widner H, Schirke N, Ortel W, Del Sorbo F, Albanese A, Pellecchia MT, Barone P, et al: Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. Mov Disord 2010, 25:1204–12.
6. Wenning GK, Geser F, Kistler F, Seppi K, Duaver S, Boesch S, Kollensperger M, Goebel G, Pfeiffer KP, Barone P, Pellecchia MT, Quinn NP, Kockenent V, Fowler CJ, Schrag A, Mathias CJ, Giladi N, Gurevich T, Dupont E, Ortel W, Nilsen CF, Widner H, Ortel W, Eggert KM, Albanese A, del Sorbo F, Tolsa E, Barone P, Deuschl G, Hellriegel H, et al: The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurology 2013, 12:264–74.
7. Yabe I, Soma H, Taka I, Fujiki N, Yanagihara T, Sasaki H: MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA. J Neurol Sci 2006, 249:115–21.
8. Ben-Shlomo Y, Wenning GK, Tison F, Quinn NP: Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. Neurology 1997, 48:384–93.
9. Schrag A, Wenning GK, Quinn N, Ben-Shlomo Y: Survival in multiple system atrophy. Mov Disord 2008, 23:294–6.
10. Pado M, Kahn J, Lantois PL: Gialt cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989, 94:79–100.
11. Graham JS, Oppenheimer DR: Orhthostatic hypotension and nicotin sensitivity in a case of multiple system atrophy. J Neurol Neurosurg Psychiatry 1969, 32:28–34.
12. Wenning GK, Tison F, Elliott L, Quinn NP, Daniel SE: Olivopontocerebellar pathology in multiple system atrophy. Mov Disord 1996, 11:157–62.
13. Ozawa T, Paviour D, Quinn NP, Josephs KA, Sangha H, Killford L, Healy DG, Wood NW, Lees AJ, Holton JL, Revess T: The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain 2004, 127:2657–71.
14. Jellinger KA, Seppi K, Wenning GK: Grading of neuropathology in multiple system atrophy: proposal for a novel scale. Mov Disord 2005, 20:529–36.
15. Jecmenica-Lukic M, Poewe W, Tolsa E, Wenning GK: Predmotor signs and symptoms of multiple system atrophy. Lancet Neurol 2012, 11:361–8.
16. Crespo-Miguel, Berardos CE: Central control of autonomic function and involvement in neurodegenerative disorders. Handb Clin Neurol 2013, 117:45–57.
17. Kuzdas-wood D, Stefanova N, Jellinger KA, Seppi K, Schlossmacher MG, Poewe W, Wenning GK: Towards translational therapies for multiple system atrophy. Prog Neurobiol 2014, 118C:19–35.
18. Orimo S, Kanazawa T, Nakamura A, Uchihara T, Mori F, Kikita A, Wakabayashi K, Takahashi H: Degeneration of cardiac sympathetic nerve can occur in multiple system atrophy. *Acta Neuropathol* 2007, 113:81–8.

19. Sakakibara R, Hattori T, Uchiyama T, Yamashita T: Videodynamic and sphincter motor unit potential analyses in Parkinson’s disease and multiple system atrophy. *J Neurol Neurosurg Psychiatr* 2001, 71:60–6.

20. Sone M, Yoshida M, Hashizume Y, Hishikawa N, Sobue G: alpha-Synuclein-immunoreactive structure formation is enhanced in sympathetic ganglia of patients with multiple system atrophy. *Acta Neuropathol* 2005, 110:19–26.

21. Provetera V, Nolano M, Caporaso G, Stancanelli A, Manganelli F, Iodic R, Selim MW, De Rosa A, Lanzillo B, Pellecchia MT, De Michele G, Santoro L: Postganglionic sudentor demenrter in patients with multiple system atrophy. *Neurology* 2014, 82:2223–9.

22. Arima K, Ueda K, Sunohara N, Arakawa K, Hirai S, Nakamura M, Tonozuka-Uehara H, Kawai M: NACP/alpha-synuclein immunoreactivity in fibrillary components of neuronal and oligodendrogial cytoplasmic inclusions in the pontine nuclei in multiple system atrophy. *Acta Neuropathol* 1998, 96:639–44.

23. Spillantini MG, Crowther RA, Jäker R, Cairns NJ, Lantos PL, Goedert M: Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson’s disease and dementia with Lewy bodies. *Neurosci Lett* 1998, 251:205–8.

24. Tu PH, Galvin JE, Baba M, Giasson B, Tomsick T, Trojanowski JQ, Lee VM: Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble alpha-synuclein. *Ann Neurol* 1998, 44:45–52.

25. Wakabayashi K, Yoshimoto M, Tsuji S, Takahashi H: alpha-Synuclein immunoreactivity in glial cytoplasmic inclusions in multiple system atrophy. *Neurosci Lett* 1998, 249:180–2.

26. Trojanowski JQ, Revesz T: Proposed neuropathological criteria for the post-mortem diagnosis of multiple system atrophy. *Neuropathol Appl Neurobiol* 2007, 33:615–20.

27. Gilman S, Werning KG, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dujovne C, Hajrani H, Klockgether T, Lees AJ, Poewe W, Revesz T, Robertson D, Sandroni P, Seppi K, Vidal-Ortiz A, Munsat TL: Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008, 70:670–6.

28. Papp M, Lantos PL: The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. *Brain* 1994, 117:235–43.

29. Song YJ, Lundvig DM, Huang Y, Gai WP, Blumbergs PC, Hajrani H, Otzen DE, Halliday GM, Jensen PH: p25alpha relocalizes in oligodendroglia from myelin to cytoplasmic inclusions in multiple system atrophy. *Am J Pathol* 2007, 171:1291–303.

30. Linderos E, Lundvig D, Petersen C, Madsen P, Petersen C, Madsen P, Nyengaard JR, Højrup P, Sorensen AG, Halliday GM, Jensen PH: Myelin to cytoplasmic inclusions in multiple system atrophy. *Acta Neuropathol* 2007, 114:76–82.

31. Braak H, Rüb U, Del Tredici K: Involvement of precerebellar nuclei in Parkinson’s disease and multiple system atrophy. *Ann Neurol* 2005, 57:110:7–16.

32. Scotti A, Cacchione F, Grammatico M, Tortora G, Scicolone M, Balsamo R, Cilia G, Marra M, Impagliazzo AR, Fratta P, Carbone D, Del Turco F, D’Alessio R, Chiappini E: The distribution of oligodendroglial inclusions in familial and sporadic multiple-system atrophy. *N Engl J Med* 2013, 369:233–44.

33. Blin O, Desnuelle C, Roscal O, Borg M, Peyro Saint Paul H, Azulay JP, Billi F, Figarella D, Coulor F, Pellissier JF, et al: Mitochondrial respiratory failure in skeletal muscle from patients with Parkinson’s disease and multiple system atrophy (abstract). *J Neurol Sci* 1994, 125:95–101.

34. Yamashita T, Ando Y, Obaishy K, Teraizaki H, Sakashta N, Uchida K, Ohara E, Ando M, Uchino M: Oxidative injury is present in Purkinje cells in patients with olivopontocerebellar atrophy. *J Neurol Sci* 2000, 175:107–10.

35. Neidt M, Goldbaum O, Richter-Landsberg C: alpha-Synuclein promotes the recruitment of tau to protein inclusions in oligodendrogial cells: effects of oxidative and proteolytic stress. J Mol Neurosci 2009, 39:266–34.

36. Stefanova N, Reindl M, Neumann M, Haass C, Poewe W, Kaipel PJ, Wenning GK: Oxidative stress in transgenic mice with oligodendrogial alpha-synuclein overexpression replicates the characteristic neuropathology of multiple system atrophy. Am J Pathol 2005, 166:869–76.

37. Younessi E, Scheller C, Tribi F, Reederer P: Degeneration of neuronal cells due to oxidative stress-microglial contribution. Pankinsonism Relat Disord 2002, 8:401–6.

38. Vilhardt F: Microglia: phagocyte and glia cell. Int J Biochem Cell Biol 2005, 37:17–21.

39. Stefanova N, Reindl M, Neumann M, Kaipel PJ, Poewe W, Wenning GK: Microglial activation mediates neurodegeneration related to oligodendrogial alpha-synucleinopathies: implications for multiple system atrophy. Mov Disord 2007, 22:1916–203.

40. Budde K, Winge K, Agander TK, Pakkenburg B: Screening of Toll-like receptors expression in multiple system atrophy brains. *Neurochem Res* 2013, 38:1252–9.

41. Amor S, Puentes F, Baker D, Van der Valk P: Inflammation in neurodegenerative diseases. *J Neurol Neurosurg Psychiatr* 2010, 129:154–69.

42. Stefanova N, Fellner I, Reindl M, Marsik F, Poewe W, Wenning GK: Toll-like receptor 4 promotes α-synuclein clearance and survival of nigral dopaminergic neurons. *J Neurol Sci* 2011, 179:954–63.

43. Wullner U, Abele M, Schmitz-Huebsch T, Wilhelm K, Benecke R, Deuschl G, Klockgether T: Probable multiple system atrophy in a German family. J Neurol Neurosurg Psychiatr 2004, 75:924–8.

44. Soma H, Yabe I, Takei A, Fujiki N, Yanagihara T, Sasaki H: Heredity in multiple system atrophy. *J Neuros Surg* 2006, 240:107–10.

45. Kara K, Mosem Y, Tokiguchi S, Shimohata M, Terajima K, Onodera O, Kakita A, Yamada M, Takahashi H, Hirasawa M, Mizuno Y, Ogata K, Goto J, Kanazawa L, Ichinawashi M, Tsuji S: Multiplex families with multiple system atrophy. *Arch Neurol* 2007, 64:545–51.

46. Al-Chalabi A, Dürr A, Wood NW, Parkison MH, Camuzat A, Hulot JS, Morris KE, Renton A, Sussmund SJ, Landeweherm BG, Ludolph A, Argy J, Bricc A, Leagh PN, Bensinger G, NINPS Genetic Study Group: Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. *Plos One* 2009, 4(e7114).

47. Scholz RW, Houlden H, Schulte C, Sharma M, Li A, Berg D, Melchers A, Paudel R, Gibbs JR, Simon-Sanchez J, Paia-Ruiz C, Bjas C, Jing D, Chen H, Trumay E, Aneppall S, Zonosi RR, Revesz T, Holton J, Wood N, Lees A, Oeletel W, Wullner U, Goldswurm S, Pellicchia MT, Blt D, Riess O, Fernandes HH, Rodriguez RL et al: SNCA variants are associated with increased risk for multiple system atrophy. *Ann Neurol* 2009, 65:610–4.

48. Keeley AP, Asa YT, Kata E, Limousin P, Ling H, Lewis P, Proukakis C, Quinn N, Revesz T, Wharton SB, Lees AJ, Revesz T, Houlden H, Holton J: α-Synucleinopathies associated with G51D SNCA mutation: a link between Parkinson’s disease and multiple system atrophy? *J Neurol Neurosurg Psychiatr* 2009, 80:1253–9.

49. Shibao C, Garland EM, Gamboa A, Venkatesh-Jones CL, Van Woeltz M, Haines JL, Yu C, Biaggioni I: PRRN1259V homozygosity in multiple system atrophy versus Parkinson’s disease. *Clin Auton Res* 2008, 18:1–9.

50. Miller DW, Johnson JM, Solano SM, Hollingsworth ZR, Standaert DG, Young AB: Absence of alpha-synuclein mRNA expression in normal and multiple system atrophy oligodendroglia. J Neurol Neurosurg Psychiatr 2005, 112:163–73.

51. Asa YT, Simpson JE, Heath PR, Wharton SB, Lees AJ, Revesz T, Houlden H, Holton J: α-Synuclein mRNA expression in oligodendrocytes in MSA. *Glia* 2014, 62:220–30.
142. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, Kaufmann H, Klockgether T, Lang AE, Lantos PL, Litvan I, Mathias CJ, Oliver E, Robertson D, Schatz I, Wenning GK: Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999, 163:94–8.

143. Colosimo C, Inghilleri M: A further case of nicotine sensitivity in multiple system atrophy. Clin Neuropharmacol 2012, 35:51–2.

144. Winge K, Fowler CJ: Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. Mov Disord 2006, 21:373–45.

145. Shannon JR, Diedrich A, Biaggioni I, Tark J, Robertson RM, Robertson D, Jordan J: Water drinking as a treatment for orthostatic syndromes. Am J Med 2002, 112:55–60.

146. Low PA, Singer W: Management of neurogenic orthostatic hypotension: an update. Lancet Neurol 2008, 7:451–8.

147. Hauser RA, Hewitt LA, Isaacson S: Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson’s disease (NOH306A). J Parkinsons Dis 2014, 4:57–65.

148. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA: Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Middorine Study Group. JAMA 1997, 277:1046–51.

149. Raimbach SJ, Cortelli P, Kooner JS, Bannister R, Bloom SR, Mathias CJ: Efficacy and safety of rifampicin for multiple system atrophy: a randomized, double-blind, placebo-controlled trial. Mov Disord 2007, 22:1138–44.

150. Bensimon G, Ludolph A, Agid Y, Vidalhelmet M, Payan C, Leigh PN, NNIPPS Study Group: Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. Brain 2009, 132:2656–71.

151. Dodel R, Spottke A, Gerhard A, Reuss A, Reinecker S, Schimke N, Geser F, Kollensperger M, Seppi K, Klass M, Krause M, Daniels C, Deuschl G, Böttger S, Naumann M, Lipp A, Gruber D, Kupsch A, Du Y, Turkheimer F, Brooks DJ, Klockgether T, Poeewe W, Wenning G, et al: Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C] (R)-PK11195 PET (MEMSA-trial). Mov Disord 2010, 25:97–107.

152. Low PA, Robertson D, Gilman S, Kaufmann H, Singer W, Biaggioni I, Freeman R, Petman S, Hauser RA, Cheshire W, Lessig S, Vemino S, Mandrekar J, Dupont WD, Chellinsky T, Galpem WR: Efficacy and safety of rifampicin for multiple system atrophy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014, 13:768–75.

153. Saccà F, Marsili A, Quarantelli M, Brescia Morra V, Brunetti A, Carbone R, Pane C, Puorro G, Russo CV, Salvatore E, Tucci T, De Michele G, Filla A: A randomized clinical trial of lithium in multiple system atrophy. J Neurol 2013, 260:658–61.

154. Lee PH, Lee JE, Kim HS, Song SK, Lee HS, Nam HS, Cheong MJ, Jeong Y, Park HK, Kim DJ, Nam CM, Lee JD, Kim HO, Sohn YH: A randomized trial of mesenchymal stem cells in multiple system atrophy. Ann Neuro 2012, 72:32–40.

155. Aktas O, Zipp F: Regulation of self-reactive T cells by human immunoglobulins—implications for multiple sclerosis therapy. Curr Pharm Des 2003, 9:245–56.

156. Novak P, Williams A, Rayin P, Zukiya O, Abduljallil A, Novak V: Treatment of multiple system atrophy using intravenous immunoglobulin. BMC Neurol 2012, 12:131.

157. Geser F, Wenning GK, Seppi K, Stampfer-Kountchev M, Scherfler C, Sawires M, Frick C, Ndayisaba JP, Ulmer H, Pellecchia MT, Barone P, Kim HT, Hooker J, Quinn NP, Caidoza A, Tolosa E, Abele M, Klockgether T, Østergaard K, Dupont E, Schimke N, Eggert KM, Oetzel W, Djaldeiti R, Poeewe W, European MSA Study Group: Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA Study Group (EMSA SG). Mov Disord 2006, 21:179–86.

158. Kriner F, Jellinger KA, Scholz SW, Seppi K, Stefanova N, Antonini A, Poeewe W, Wenning G: Multiple system atrophy as emerging template for accelerated drugs discovery in a-synucleinopathies. Parkinsonism Relat Disord in press.

159. Quinn N: Multiple system atrophy—the nature of the beast. J Neurol Neurosurg Psychiatr 1989, Suppl:78–89.

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