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Review

Symptomatic therapy of multiple system atrophy

Guido Rohrer[a], Günter U. Höglinger[b,c,*], Johannes Levin[a,b,**]

[a] Department of Neurology, Ludwig-Maximilians-Universität München, Munich, Germany
[b] German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
[c] Department of Neurology, Technical University Munich, Munich, Germany

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ABSTRACT

Multiple system atrophy is a progressive neurodegenerative disease characterized by the association of autonomic failure and a movement disorder that consist of either a hypokinetic movement disorder or a cerebellar syndrome or both. In addition to these core characteristics other movement disorders (e.g. dystonia, myoclonus, spasticity), and neuropsychiatric symptoms (e.g. depression, cognitive dysfunction) may occur in the course of the disease and can severely impair patients' quality of live. To date no causal therapy is available and therefore symptomatic treatment plays a pivotal role in patient care. In this article we provide an overview of frequent clinical symptoms and their symptomatic treatment options.

1. Introduction

Multiple system atrophy (MSA) is an adult onset, devastating, progressive neurodegenerative disease with a mean survival of 6 to 10 years from symptom onset (Fanciulli and Wenning, 2015). MSA is a slowly progressive disease characterized by the association of autonomic failure and a variety of movement disorders including parkinsonism and/or cerebellar ataxia as key features, but also dystonic and pyramidal symptoms. According to the predominant motor symptoms two subtypes have been described, characterized by either a hypokinetic-rigid parkinsonian syndrome (MSA-P) or a cerebellar syndrome (MSA-C). In both subtypes, autonomic dysfunction such as orthostatic hypotension, urinary incontinence or erectile dysfunction is required to establish the diagnosis of clinically possible or probable MSA according to current diagnostic criteria (Gilman et al., 2008). Especially autonomic symptoms have been described to severely impact the quality of life of MSA patients (Köllensperger et al., 2010).

Another frequent symptom of MSA is occurrence of neuropsychiatric symptoms including depression (Schrag et al., 2006; Schrag et al., 2010). Cognitive impairment and dementia have been described in MSA, although being a non-supporting feature in current diagnostic criteria (Stankovic et al., 2014). At present, no casual treatment for disease modification is available. Therefore, symptomatic treatment is of pivotal importance in patient care along the course of the disease. In this article we provide an overview of the symptomatic treatment options of the most relevant symptoms in MSA. Treatment options for MSA symptoms are displayed in Table 1.

2. Motor features

Motor features in MSA are characterized by a predominant hypokinetic-rigid syndrome in MSA-P, a predominant cerebellar syndrome in MSA-C and other types of movement disorders such as focal dystonia, which can be present both in MSA-C and MSA-P (Levin et al., 2016).

2.1. Parkinsonism

Hypokinesia, rigidity and early tendency to fall characterize the core motor features of MSA-P and can be observed at least to some extent in 87% of all cases (Köllensperger et al., 2010). Approximately one third of patients may respond to levodopa although benefit is temporarily limited and often markedly less pronounced than in patients with PD (Constantinescu et al., 2007; Köllensperger et al., 2010; Schrag et al., 2006). A poor levodopa response is one diagnostic feature of possible and probable MSA-P and may therefore be used to differentiate MSA-P from PD (Gilman et al., 2008). Although there is low evidence for the use of levodopa, its use is strongly supported by a broad clinical experience. Levodopa in daily doses up to 1 g is considered as first line therapy (Flabeau et al., 2010). Unresponsiveness to levodopa should only be accepted after a treatment period of at least

* Correspondence to: G. Höglinger, Technical University Munich, Department of Neurology & German Center for Neurodegenerative Diseases (DZNE) e.V., Feodor-Lynen-Straße 17, 81377 Munich, Germany.
** Correspondence to: J. Levin, Ludwig-Maximilians-Universität München, Department of Neurology & German Center for Neurodegenerative Diseases (DZNE) e.V., Marchioninistraße 15, 81377 Munich, Germany.
E-mail addresses: guenter.hoeglinger@dzne.de (G.U. Höglinger), Johannes.Levin@med.uni-muenchen.de (J. Levin).

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Table 1

Symptoms	Pharmacological interventions	Nonpharmacological interventions
Motor symptoms		
Parkinsonism	Levodopa up to 1000 mg/d Amantadine 100–200 mg up to 3 × /d	Physiotherapy Occupational therapy Speech therapy
Cerebellar ataxia		Physiotherapy Occupational therapy Speech therapy
Dystonia	Botulinum toxin A	
Autonomic failure		
Urinary dysfunction		
Urge incontinence	Oxybutinin 2.5–5 mg 2–3 × /d Injections of Botulinum toxin A into the detrusor muscle	Intermittent or permanent urethral or suprapubic catheterization
Incomplete bladder emptying	Moxisylyte 10 mg 3 × /d Prazosin 1 mg 3 × /d	
Nycturia	Desmopressin 10–40 µg intranasal spray once at night	
Erectile dysfunction	Sildenafil 50 mg–100 mg	
Orthostatic hypotension	Ephedrine 15–45 × 3mg/d	Elastic stockings
Postprandial hypotension	Fludrocortisone 0.1–0.4 mg/d Midodrine 2.5–10 mg 3 × /d L-threo-DOPS 600 mg 2 × /d Octreotide 25–50 µg s.c. 30 min before meals	Adequate salt and fluid intake Head-up tilt during night
Neuropsychiatric manifestations		
Depression	SSRIs	Psychotherapy
Sleep disorders		
REM-sleep behavior disorder	Clonazepam 0.5–2 mg/d Melatonin 2 mg/d Gabapentin 300–800 mg/d Pregabalin 75–100 mg/d Sodium oxybate 4.5–9 g/d	
Nocturnal stridor		Non-invasive positive pressure ventilation (NPPV) Continuous positive airway pressure (CPAP) Tracheostomy

3 months without any significant clinical improvement (Gilman et al., 2008). Levodopa response may be objectified by improvement of 30% or more on part II of the Unified Multiple System Atrophy Rating Scale (UMSARS)(Wenning et al., 2004). Withdrawal of medication in patients without apparent clinical benefit may lead to an individual deterioration and justify continuation of treatment (Fanciulli and Wenning, 2015). Results of treatment with dopamine agonists have been disappointing as they show poor efficacy and may involve severe side effects, particularly worsening of orthostatic hypotension. Therefore dopamine agonists are not considered as a therapeutic option (Flabeau et al., 2010; Wenning et al., 1994).

Amantadine may be considered as an alternative or additional treatment option for parkinsonism (2–3 × 100–200 mg daily). Amantadine showed a trend towards reduction of motor symptoms in anecdotal reports without providing clinically significant anti-parkinsonian benefit in a placebo-controlled trial (Köllensperger et al., 2010; Rajrut et al., 1997; Wenning et al., 2005b). Side effects may include leg edema, livedo reticularis and confusion, especially when doses of more than 300 mg daily are used (Dutra and Vasconcellos, 2014; Hauser et al., 2017).

As pharmaceutical strategies are of limited efficacy, non-pharmacological treatment options such as physiotherapy and occupational therapy play important roles in improving symptoms and patients quality of life. 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 (Jain et al., 2004). No controlled trials for physiotherapy are available so far. However, as motor function can be improved by physiotherapy in Parkinson's disease (Tomlinson et al., 2013), patients with MSA-P with predominant Parkinsonism as predominant motor feature may also benefit (Colosimo et al., 2005). Also physical support including canes, walkers or wheelchairs will be an option to support patients with severe movement disorders.

In PD, deep brain stimulation has been used very efficiently to improve motor symptoms and quality of daily life (Dams et al., 2013; Deuschl et al., 2006). In contrast, data from case reports and small case series in MSA patients evidence ineffectiveness of deep brain stimulation on motor symptoms in MSA (Chou et al., 2004; Lezcano et al., 2004; Meissner et al., 2016).

2.2. Cerebellar syndrome

To date no efficient drug treatment is available for cerebellar symptoms such as gait ataxia, scanning dysarthria, ataxia of the limbs, intention tremor and oculomotor dysfunction.

Intensive physiotherapy as well as resistance training and challenge-oriented gait and balance training improve coordination, balance, gait and function in degenerative cerebellar disorders (Giannantoni et al., 2009; Ilg et al., 2014; Ilg et al., 2009; Landers et al., 2009; Wedge, 2008) and is therefore often integrated in the therapeutic concept. Patients with scanning dysarthria and impairment of swallowing may benefit from speech therapy (Colosimo et al., 2005).

2.3. Dystonia

Focal dystonia, e.g. cervical dystonia (antecollis), blepharospasm and limb dystonia, is common in MSA-P. Reports on prevalence vary from 12% to 46% (Boesch et al., 2002; Wenning et al., 1997).

Botulinum toxin injections may reduce dystonic symptoms and is described to be particularly effective in the treatment of blepharospasm. Furthermore, botulinum toxin may alleviate impaired function of dystonic limb in early disease stages (Müller et al., 2002).

Treatment of cervical dystonia with botulinum toxin injections is currently being regarded as potentially harmful, as severe transient dysphagia may occur. For this indication botulinum toxin should therefore be applied with caution (Thobois et al., 2001).