



## Mini Review

# Multiple System Atrophy: An Update Review

**Jacques De Reuck\***

Department of Neurology, University Hospital, Ghent, Belgium

\*Corresponding author: Jacques De Reuck, Department of Neurology, University Hospital, Ryvissche park 16, 9052 Zwijnaarde, Belgium.

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## Abstract

Multiple system atrophy is a progressive fatal neurodegenerative disease, characterized alpha-synuclein accumulation mainly in oligodendroglial cells of the white matter and to a lesser degree in neurons. Autonomic and urogenital failures are the dominant clinical features. The disease is subdivided in a predominant parkinsonian type and in a predominant cerebellar atactic type. The parkinsonian type represents 80% of the patients while the cerebellar type is found in 20% of the cases. Smoking is less frequent in patients with the parkinsonian type of multiple system atrophy. On magnetic resonance imaging middle cerebellar peduncle atrophy and hyper intensity, putaminal hypointensity and hyperintense putaminal rim in addition to pons hot bun sign and atrophy are the main features. No protective treatment is available. Only supportive measures can be proposed.

**Keywords:** Multiple system atrophy; Alpha-synuclein; Parkinsonian type; Cerebellar atactic type; Parkinson's disease; Dementia with Lewy bodies

**Abbreviations:** **MSA:** Multiple System Atrophy; **MCA-P:** Parkinsonian type of Multiple System Atrophy; **MCA-C:** Cerebellar type of Multiple System Atrophy; **PD:** Parkinson's disease

## Introduction

The new criteria retain the diagnostic categories of Multiple System Atrophy (MSA) with predominant Parkinsonism features (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) to designate the predominant motor features and also the designations of definite, probable, and possible MSA [1].

Alpha-synuclein is observed in oligodendroglial cytoplasmic inclusions of the cerebral white matter in MSA brains. This protein may be responsible to form filaments that aggregate into cytoplasmic inclusions, contributing to the dysfunction or death of glial cells as well as neurons in the different MSA phenotypes [2]. Using cryo-electron microscopy, two different types of alpha-synuclein inclusions are observed, each of which consists of two different protofilaments [3].

Synucleinopathies include not only multiple system atrophy but also Parkinson's Disease (PD) and dementia with

Lewy bodies due to the presence of alpha-synuclein aggregates throughout the nervous system. However, they diverge from one another with regards to their clinical and pathological phenotype. Although there are many similarities of the alpha-synuclein pathology between MSA and PD, the former is significantly more potent in inducing motor deficits and degeneration of the striatum. The more widespread spreading of the alpha-synuclein pathology and inflammation reflects the more aggressive nature of MSA [4]. Perturbed iron homeostasis is a potential factor in the pathogenesis in MSA-associated neurodegeneration [5].

A controversial topic in MSA is the non-supporting feature of the association of cognitive impairment from both clinical and pathological perspectives [6,7].

## Multiple System Atrophy with Predominant Parkinsonian Features

The interval from initial symptom to combined motor and autonomic dysfunction predicts the functional deterioration and survival in MSA patients. MSA-P patients have more rapid functional deterioration than the MSA-C ones. Isolated autonomic failure and REM sleep behavior disorder are common premotor features of MSA [8]. MSA is dominated by autonomic and urogenital failure. The MSA-P type represents 80% [9].

On Magnetic Resonance Imaging (MRI) the hyperintense rim at the lateral edge of the dorsolateral putamen is observed in

34.5% and the hot cross bun sign in the pontine basis in 63.3% [7]. Putaminal iron accumulation is a secondary by-product of the neurodegenerative atrophy [10].

Patients with MSA-P show normal neuromelanin in the substantia nigra and the locus coeruleus, similar to normal brains and allowing the distinction compared to idiopathic Parkinson ones [11]. The pontine hot-cross bun is of lower visual grade in MSA-P than in MSA-C on T2\*weighted imaging [12].

The incidence of smokers is significantly lower in the MSA-P patients than in other non-Parkinson related diseases [13]. Rare MSA-P cases can be associated to adult polyglucosan body disease [14].

### Multiple system atrophy with predominant cerebellar features.

The MSA-C represents approximately 20% of the whole disease group [9]. Middle cerebellar peduncle atrophy and hyperintensity, hot bun sign, putaminal hypointensity and hyperintense putaminal rim in addition to pons atrophy are the main features [15].

The alpha-synucleinopathy of the oligodendroglial cells involves mainly the olivopontocerebellar and the autonomic nervous systems, but also to a lesser degree other parts of the central and peripheral nervous systems [16,17].

DAT-scan imaging with loflupane123 injection, however, reveals bilateral nigro-striatal degeneration in possible MSA-C, due to a decreased uptake of dopamine transporters [18].

### Therapeutical Options

There are many drug trials in MSA. Most studies include those for relieve of parkinsonian motor symptoms, autonomic dysfunction, and depression [19].

Only one third of MSA patients may benefit from dopamine for symptomatic treatment of parkinsonism, whereas physiotherapy remains the best therapeutic option for cerebellar ataxia. Many curative treatment trials are available for MSA [20]. In a small series of MSA patients, receiving amantadine 200 mg twice daily, there is a trend of reduction of the parkinsonian symptoms [21].

A preliminary study shows that intravenous amantadine is a safe and effective treatment in MSA-P. However still an additional double-blind placebo-controlled study is needed to confirm these results [22].

Riluzole is generally well tolerated but there are no significant anti-parkinsonian effects. Treatment with 1 mg riluzole daily do not improve the population of patients with MSA-P [23]. A treatment with 1 mg rasagiline daily does not improve the population of patients with MSA-P [24].

In a mouse model of MSA rifampicin inhibits the formation alfa-synuclien fibrils. That is why a double-blind study in MSA patients was started at a dose of two times 300 mg daily. Rifampicin did not slow or halt the progression of the disease [25].

Polyphenol epigallocatechin gallate inhibits alpha-synuclein aggregation and reduces associated toxicity. However, 48 weeks of treatment do not modify disease progression in patients with MSA. Epigallocatechin gallate is overall well tolerated but hepatotoxic effects are observed in some patients [26].

### Conclusions

Multiple system atrophy is a fatal progressive neurodegenerative disease for which no conclusive protective treatment is available. Only supporting measures can be proposed.

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