# MULTIPLE SYSTEM ATROPHY - ETIOLOGY, SUBTYPES AND CLINICAL PROBLEMS

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S u m m a r y. Multiple Systemic Atrophy (MSA) is a neurodegenerative disease characterized by concomitant parkinsonian symptoms of varying intensity, cerebral, autonomic and pyramidal disorders, an atrophy of neurons as well as glial cytoplasmatic  $\alpha$ -synuclein inclusions in the oligodendrocytes. It is a rare disease with an incidence of 3:100 000. Three types of MSA are distinguished: MSA-P (MSA with dominance of parkinsonism), MSA-C (MSA with predominance of cerebellar ataxia), and MSA-A (MSA with predominance of the autonomic system dysfunctions). The study presents a review of research reports on MSA. We focus on the literature about α-synucleinopathy, mainly MSA-C and MSA-P. The etiology, pathogenesis and clinical problems in MSA are discussed. The last decade has brought increased interest in MSA among clinical researchers. There are many ongoing trials to better understand MSA pathogenesis, and to develop effective treatment

K e y w o r d s: neurodegeneration,  $\alpha$ -synucleinopathy, multiple system atrophy.

## **INTRODUCTION**

Multiple Systemic Atrophy (MSA) is a neurodegenerative disease characterized by the coexistence of various intensity parkinsonian symptoms, and cerebral, autonomic and pyramidal disorders [1, 2, 3, 4]. It is characterized by neuronal atrophy as well as glial cytoplasmatic  $\alpha$ -synuclein inclusions in the oligodendrocytes [4, 5, 6, 7]. It is a rare disease with an incidence of 3:100 000 [3, 8, 9, 10]. MSA is the second to progressive supranuclear palsy, most common form of atypical parkinsonism [11]. Three types of MSA are distinguished: MSA-P (MSA with dominating parkinsonism), MSA-C (MSA with predominance of cerebellar ataxia), and

MSA-A (MSA with predominance of the autonomic system dysfunctions) [12].

## MATERIALS, METHODS AND AIM

The work is based on the review of research reports on MSA, i.e.  $\alpha$ -synucleinopathy, mainly MSA-C and MSA-P which discuss the etiology, pathogenesis and clinical problems related to MSA treatment.

#### A brief history of MSA

The history of MSA begins in 1900, when two French doctors, Dejerine and André-Thomas, described a new disease entity, which they called the 'olivopontocerebellar atrophy (OPCA). OPCA is a neurodegenerative syndrome characterized by prominent cerebellar and extrapyramidal signs, dysphagia and dysarthria [13]. The French doctors studied two cases and found that their symptoms (mainly cerebellar symptoms) as well as the results of histopathological examination differ from the clinical picture of neurological diseases described so far [14].

In 1960 Milton Shy with Glen Drager presented two patients with similar symptoms, mainly orthostatic hypotension. As the disease progressed, parkinsonism symptoms appeared. It was found that these patients suffered from the same disease, and the term 'Shy-Drager Syndrome' (SDS) was introduced [15]. In the same year 'striatonigral degeneration' (SND) was described. Patients suffering from SND had prevailing parkinsonism aside cerebellar ataxia and autonomic dysfunctions [16].

The breakthrough came in 1969, when Graham and Oppenheimer noticed that all of the three previously described diseases have similar manifestations and pathological changes in the brain. They introduced the term 'Multiple System Atrophy', which includes the OPCA, SDS and SND [17]. In 1998, First MSA Consensus proposed that patients diagnosed with OPCA should be classified as suffering from MSA-C, while patients with SDS and SND as MSA-P [18].

# **Etiology of MSA**

The etiology of MSA has not been fully elucidated. MSA is considered to be a sporadic disease in which both genetic and environmental factors are involved [1, 3]. It is suspected that the exposure to organic solvents and pesticides as well as smoking may increase the risk of developing MSA [19, 20]. The influence of genetic factors on the development of MSA is also indicated by cases of familial occurrence of systemic atrophy, which were observed in Germany, Japan and in the USA [4, 12, 21, 22, 23]. Studies have shown that in the Japanese population there is a link between the occurrence of the V393A allele (as well as other defective alleles) of COO2 gene (coenzyme Q2 gene, an enzyme involved in the synthesis of coenzyme Q10) and the incidence of MSA. V393A allele frequency in the healthy Japanese population is of 1.6% to 2.2%. Among patients with MSA V393A allele occurred in 4.8% of all examined alleles. In addition, in MSA patients with the defective gene, a higher percentage of subtype C (87%) was found compared to patients without defective alleles (70%). The presence of defective alleles has not been reported in Europe and North America. The authors stated that the described mutations may be one of many genetic factors affecting the incidence of MSA. The obtained results also indicate that the difference in the incidence of MSA subtypes is most likely due to genetic factors. The authors of the described study also suggested that CoQ10 supplementation may be helpful in the treatment of MSA caused by its deficiency in people with mutated COQ2 gene [21].

#### Pathogenesis of MSA

MSA is classified as  $\alpha$ -synucleinopathy, a group of diseases like Parkinson's disease and dementia with Lewy bodies [5]. In the course of MSA, abnormal a-synuclein deposition protein in the brain tissue is observed. These deposits are mainly located in the cytoplasm of glial cells (oligodendrocytes), and are called Papp-Lantos bodies (glial cytoplasmic inclusions, GCls,). These inclusions are not found in other  $\alpha$ -synucleinopathies, and are characteristic of MSA [4, 5, 24, 25, 26]. Other changes observed in MSA include glial nuclear inclusions (GN), Lewy bodies in the neurons, neuronal atrophy and axonal degeneration [5]. These changes are located in the cerebellum, striatum, substantia nigra, dorsal nucleus of the vagus nerve and other catecholaminergic nuclei in the medulla, locus coeruleus, hypothalamus and the intermediolateral nuclei [5, 27].

Recent studies have shown that oxidative stress may be an important contributor in pathogenesis of MSA. The induction of oxidative stress in the brain tissue of mice led to occurrence of MSAspecific lesions [28, 29]. Another study found that people exposed to oxidative stress, such as nonsmokers (nicotine reduces oxidative stress in the brain tissue) or those exposed to plant protection products are more likely to suffer from multiple system atrophy [20].

In 2015, a research group led by Stanley B. Prusiner found that MSA might be transmitted via prions. Researchers implanted a brain homogenate of patients who died from MSA into the brain tissue of TgM83 +/- mice. It turned out that all mice developed MSA within 120 days from surgery. The mice used were carriers of the A53 mutation of  $\alpha$ -synuclein gene [6]. This hypothesis, although formulated by the eminent Nobel Prize winner, has some drawbacks. It has been reported that in the mice without A53 mutation, after similar procedure, MSA did not occur. In prion diseases, such as Creutzfeldt-Jakob disease (CJD), after implanting the homogenate of the brain tissue taken from a person who died from CJD to wild-type mice, the disease occurs. In addition, after the neuropathological study of the rodent brains in which MSA occurred, it was found that  $\alpha$ -synuclein deposits were located mainly in the neurons, not in the oligodendrocytes [30]. The pathogenesis of the MSA has not been fully elucidated.

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# **Diagnosis of MSA**

The current criteria for the diagnosis of MSA were developed in 2008 by the Second MSA Consensus. The diagnosis may include possible MSA, probable MSA, and definite MSA. Definite MSA can only be diagnosed on post-mortem examination after detection of Papp-Lantos bodies in the striatonigral or olivopontocerebellar structures [24]. The possible and probable MSA diagnosis criteria are included in the table 1 and 2 below.

Table 1. Criteria for diagnosis of probable and possible MSA [24, own elaboration]

Criteria for diagnosis of probable MSA	•	Sporadic, progressive disease in adult over 30 years old, characterized by: Autonomic failure involv- ing urinary dysfunction and erectile dysfunction in males or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg di- astolic and Cerebellar ataxia or parkin- sonism with a poor response to levodopa
Criteria for diagnosis of possible MSA	•	Sporadic, progressive disease in adult over 30 years old, characterized by: Cerebellar syndrome or par- kinsonism and At least one of the autonomic symptoms (bladder dysfunc- tion, erectile dysfunction, sig- nificant drop in blood pressure that does not match the crite- ria for probable MSA) and At least one of the additional features

Table 2. Additional features of possible MSA [24, own elaboration]

➤ Ad	ditional features of possible MSA:
≻ Pos	ssible MSA-P or MSA-C: Babinski sign with hyperreflexia,
stri	dor
> Pos	ssible MSA-P:
➤ fas	t-progressing parkinsonism,
≻ cer	ebellar symptoms,
> poo	or response to levodopa,
> pos	tural instability in the first 3 years of the disease,
> dys	phagia in the first 5 years of the disease,
> on	magnetic resonance imaging: atrophy of putamen, middle
cer	ebellar peduncles, cerebellum and pons
> hyp	pometabolism on FDG-PET in putamen, brainstem or cer-
ebe	llum
> Pos	ssible MSA-C:
➤ par	kinsonizm,
> on	MRI: atrophy of putamen, middle cerebellar peduncles, pons
> hyp	pometabolism on FDG-PET in putamen
➤ pre	synaptic dopaminergic deficiency on SPECT or PET

MSA manifestations include the occurrence of parkinsonian symptoms (tremor, bradykinesia, rigidity and postural instability), cerebellar symptoms (ataxia, imbalance, uncoordinated movements, speech (dysarthria), and oculomotor disorders), and autonomic symptoms (urinary problems, sexual problems, digestive difficulties, sweating abnormalities, orthostatic hypotension) [1, 2, 24, 31]. These symptoms may occur with varying severity [1, 2, 24, 31]. Two types of MSA are mainly distinguished: MSA-P (MSA with prominent parkinsonism) and MSA-C (MSA with predominance of cerebellar ataxia). Some scientists, however, distinguish the third subtype: MSA-A (MSA with predominance of dysfunction of the autonomic system) [12]. The incidence of MSA-C and MSA-P differs between the European/US, and the Japanese population. Subtype -P is more prevalent in Europe, representing 68% of all cases, the remaining 32% are patients with MSA-C. [32]. In Japan, most cases are MSA-C, which occurs in 67.4% of all cases, remaining 32.6% being MSA-P [33]. Figure 1.





Fig. 1. MSA subtypes in the European and Japanese populations [32, 33, own elaboration]

In clinical practice, MRI is often used in MSA diagnosis. In patients with MSA-C the MRI scans of the brain structures detect atrophy of the cerebellum, middle cerebellar peduncles and brainstem. Signal amplification on T2 images in the pons and middle cerebellar peduncles also occurs, which proves the degeneration of the ponto-cerebellar pathways. T2 hyperintensity in pons forms characteristic 'hot cross bun sign' seen on axial images. Cross bun sign is often seen in MSA-C, but it can occur in other diseases such as spinocerebellar atrophy type 2 and 3, parkinsonism secondary to vasculitis, and in variant of Creutzfeldt-Jakob disease (vCJD). It is also detected in the later stages of MSA-P [34, 35, 36]. In patients with MSA-P, changes are detected in the putamen, there is a decrease in T2 signal intensity, a linear region of high T2 signal surrounding the lateral aspect of the putamen ('putaminal rim sign') at T1,5. This symptom is specific to MSA-P, however, it can be seen in healthy individuals at T3 [34, 35, 36].

The disease is characterized by an aggressive course. The quality of life deteriorates rapidly, patients after about 3.5 years from the disease onset must use a wheelchair, and after 5 years they remain confined to bed. MSA is a neurodegenerative disease with an average survival time of 6-9 years from diagnosis [37]. There are no significant differences in the median survival time between MSA-P and MSA-C, which is respectively: 9.6 and 9.9 years from disease onset to death. The presence of autonomic symptoms at the time of diagnosis worsens the prognosis considerably [1, 38]. In 2007, the causes of death were examined in 21 patients with pathologically confirmed definite MSA. Causes of deaths included cardiopulmonary arrest (33.3%), urinary tract infection (23.8%), wasting syndrome (14.3%), aspiration pneumonia (9.5%), infectious pneumonia (9.5%), acute aspiration (4.8%), other (4.8%). It is characteristic that over 1/3 of deaths occurred suddenly (38.1%) from cardiac arrest or choking. It is also significant that 5 out of 6 patients with stridor died suddenly, which is 23.8% of all deaths. Wasting syndrome was mainly caused by dysphagia and resultant weight loss. The authors suggest that each patient with MSA should be examined for the signs of laryngeal stridor, neurogenic bladder dysfunction and dysphagia. Early diagnosis of these symptoms and their aggressive treatment may extend the patient's life expectancy [39, 41].

#### CONCLUSIONS

Clinically differentiating multiple system atrophy at all stages from other similar neurodegenerative disorders may be challenging [7, 31]. MSA is considered to be a sporadic disease in which both genetic and environmental factors are involved. The etiology and pathogenesis of MSA has not been fully elucidated. Diagnostic options include possible MSA, probable MSA, and definite MSA. Definite MSA can only be diagnosed in post-mortem examination after detection of Papp-Lantos bodies in the striatonigral or olivopontocerebellar structures. Two types of MSA are mainly distinguished: MSA-P (MSA with prominent parkinsonism), and MSA-C (MSA with predominance of cerebellar ataxia). Some scientists, however, distinguish MSA-A (MSA with predominance of the autonomic system manifestations). The incidence of MSA-C and MSA-P subtype differs between the European/US and the Japanese population. The last decade has brought increased interest in MSA among clinical researchers. There are many ongoing trials to better understand MSA pathogenesis, and to develop effective treatment.

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