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**Review**

# Multiple System Atrophy: Role of Coenzyme Q10

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## Abstract

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by a variable combination of autonomic failure, Parkinsonism, and ataxia. There is currently no treatment available to halt or delay progression of this disorder. Biochemically, MSA is characterized by mitochondrial dysfunction, oxidative stress, and inflammation. In the present article we have therefore reviewed the potential role of coenzyme Q10 (CoQ10) in the pathogenesis and treatment of MSA, on the basis of its role in mitochondrial function, and its antioxidant and anti-inflammatory activities, as well as its reported depletion in blood and cerebellar tissue from MSA patients.

**Keywords:** Coenzyme Q10; Multiple system atrophy; Mitochondrial dysfunction; Oxidative stress.

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## Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by a variable combination of autonomic failure, Parkinsonism, and ataxia [1]. As a consequence of the latter, MSA patients often suffer from genitourinary dysfunction and orthostatic hypotension [2]. With regard to treatment, L-dopa replacement therapy in MSA patients is less effective than in patients with Parkinson's disease (PD) [3]; paroxetine, a selective serotonin reuptake inhibitor has been shown to provide some benefit in MSA patients [4]. There is currently no treatment to halt or delay the progression of MSA. The age of onset of MSA is typically around 55-60 years of age. MSA may be difficult to distinguish clinically from other disorders, particularly PD, especially in the early stages of the disease [5]. MSA is one of a group of disorders known as synucleinopathies, characterized by deposition of abnormal misfolded alpha-synuclein proteins in the central and


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peripheral nervous system [6]. In PD, the abnormal alpha-synuclein is deposited in neurons, whist in MSA it forms glial cytoplasmic inclusions in oligodendrocytes. Histologically, selective atrophy and neuronal loss in striatonigral and olivopontocerebellar brain regions underlie the subdivision of MSA into Parkinsonian (MSA-P) and a cerebellar phenotype (MSA-C) [7]. Biochemically, MSA is characterized by depletion of coenzyme Q10 (CoQ10), which has a key role in cellular energy production. In some populations, particularly East Asian [8], the deficiency in CoQ10 levels is in turn associated with abnormalities in the gene, COQ2 which encodes the enzyme, coenzyme-Q2-polyprenyltransferas which is involved in the synthesis of CoQ10 [9]. Notwithstanding the COQ2 phenotype, the reports of decreased plasma and cerebellum CoQ10 status in MSA patients indicate evidence of impaired COQ biosynthesis, which in turn may contribute to the pathogenesis of MSA via mitochondrial dysfunction, oxidative stress, and inflammation. In the present review, we have therefore reviewed the potential role of CoQ10 in the pathogenesis and treatment of MSA.

## Coenzyme Q10

CoQ10 is an isoprenoid molecule that is synthesised by most cells of the body apart from red blood cells as its synthesis requires the presence of mitochondria [10,11]. CoQ10 has a number of key functions cellular functions including its role as an electron carrier in the mitochondrial respiratory chain (MRC) as well as its role as a cellular antioxidant [10,11]. CoQ10 has also been shown to directly regulate the expression of more than 100 genes, including ta number in involved in inflammation [12]. Most of the body's daily requirement for CoQ10 (estimated as 500mg) is provided via endogenous synthesis, with a relatively small proportion (5mg) obtained from the normal diet; optimal endogenous synthesis occurs at 20-25 years of age, followed by an ensuing decline, such that the production at 65-70 years is approximately 50% of that at 20-25 years [13,14]. The biosynthesis of CoQ10 is a complex multi-step process [15] for which mutations in at least 10 genes that encode enzymes in the CoQ10 biosynthetic pathway have been identified [11] which if impaired can result in deficit in endogenous CoQ10 status, process relevant to the pathogenesis of MSA as outlined in the following sections of this article. With regard to the importance of CoQ10 in MRC function and cellular energy supply, several lines of evidence point to impaired brain energy supply/mitochondrial dysfunction in MSA. These include the demonstration of reduced cerebral glucose metabolism in MSA patients via positron emission tomography [16], and reduced creatine phosphate levels/depleted cell energy metabolism quantified by phosphorus-31 nuclear magnetic resonance spectroscopy in MSA patients [17,18].

## CoQ10 depletion in MSA

A number of clinical studies have reported evidence of decreased CoQ10 levels in plasma, CSF (cerebrospinal fluid) or cerebellar tissues of MSA patients. As noted in the Introduction, a deficiency in CoQ10 levels may be associated with abnormalities in the COQ2 gene encoding the enzyme (coenzyme-Q2-polyprenyltransferase) involved in the


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synthesis of CoQ10, although this is not the case for all MSA patients [19]. Abnormalities in genes encoding other enzymes in the CoQ10 biosynthetic pathway have also been reported in some studies, including PDSS1 (Decaprenyl-diphosphate synthase subunit 1), COQ5 (methyltransferase), and COQ7 (5-demethoxyubiquinone hydroxylase) [20]. Thus, in a series of 44 MSA patients, Mitsui et al [21] found a significant 30% decrease in the mean plasma CoQ10 level of MSA patients compared to controls, regardless of patient COQ2 genotype. Kasai et al [22] described a significant reduction in serum CoQ10 levels, when related to cholesterol level (to account for the lipoprotein fraction of the blood), in 18 MSA patients (COQ2 genotype not specified) compared to controls; the circulatory lipoproteins, LDL (low density lipoprotein) and VLDL (very low-density lipoprotein) cholesterol act as the main carriers for CoQ10 in the blood. In a series of 40 patients with MSA (COQ2 phenotype not specified), Du et al [23] found significantly reduced CoQ1O levels in plasma compared to controls. Compta et al [24] reported also reported significantly reduced CoQ10 levels in CSF samples from a series of 20 MSA patients (COQ2 genotype not specified), compared to those in patients with related neurological disorders (PD, progressive supranuclear palsy) or controls. With regards to brain tissue, the cerebellum appears to be most affected by CoQ10 depletion. It is of note that cerebellar ataxia is a characteristic of MSA, whilst levels of CoQ10 in the human brain are reported to be lowest in the cerebellum, which may thus be selectively vulnerable to CoQ10 deficiency. Barca et al [25] found CoQ10 levels in post-mortem cerebellar tissue to be significantly decreased (by 40%) from a cohort of 12 MSA patients (without COQ2 mutations), compared to controls. Although none of the MSA patients had COQ2 mutations, there were significant decrease in the protein levels of PDSS1 and COQ5 CoQ10 biosynthetic enzymes. It is of note that CoQ10 levels in both striatal and occipital cortical samples from these MSA patients were similar to the controls. Similarly, Schottlaender et al [26] reported a significant decrease in CoQ10 levels in post-mortem cerebellum samples from a series of 20 MSA cases, compared to controls, although only by 3-5%. Hsaiao et al [20] found reduced levels of ATP, associated with reduced expression of the COQ2 and COQ7 CoQ10 biosynthetic enzymes, in disease-affected brain areas (principally cerebellum, as well as putamen) of MSA patients. Evidence of decreased MRC complex II-III activity has also been reported in the white matter of postmortem MSA patient brain samples which is thought to reflect the deficit in cerebral CoQ10 status reported in this condition since the activity of this enzyme is dependent upon the endogenous level of this isoprenoid [27]. In the absence of a COQ2 mutation the cause of CoQ10 deficiency reported in MSA patients is uncertain but it may result from oxidative stress induced catabolism of CoQ10 or the impairment of the enzymes in the biosynthetic pathway of the isoprenoid [26,27]. It is also of note that neurons cultured from MSA patients show evidence of autophagic impairment, as indicated by increased basal autophagy, reduced autophagic flux and reduced activity of the lysosomal enzymes, α-Mannosidase and β-Mannosidase [28]. Furthermore, that one of the functions of CoQ10 is the maintenance of


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normal lysosomal function via its role in maintaining the acidity of the organelle [29].

**Effect of CoQ10 supplementation in MSA**

Studies on supplementation of CoQ10 in MSA have been restricted to work in cell culture, or single patient case studies. Using neuronal cells cultured from MSA patients with and without the COQ2 mutation, Nakamoto et al [30] identified cellular dysfunction attributable to reduced CoQ10 levels, which were in part resolved via administration of exogenous CoQ10. In an MSA patient with the COQ2 mutation and in an advanced stage of the disease, Mitsui et al [31] reported high dose CoQ10 supplementation (1200mg/day) improved brain energy metabolism (as measured by cerebral oxygen metabolic rate/positron emission tomography). There is a clear rationale for the involvement of CoQ10 in the pathogenesis of MSA, and evidence from a number of clinical studies for depleted CoQ10 levels in blood or brain tissue from MSA patients. To date there has been no randomised controlled trials of supplementary CoQ10 in MSA, and this is now warranted. One issue which needs to be first resolved is the optimal formulation to enable supplementary CoQ10 to cross blood-brain barrier and access the brain [32].

**Safety of CoQ10**

The safety of CoQ10 has been confirmed in more than 200 randomized controlled clinical studies reported in the peer-reviewed medical literature, as listed on Medline. In these studies, CoQ10 supplementation has been used in the treatment of in a number of disorders with no serious adverse clinical effects being reported. However, very rarely, individuals may experience mild gastrointestinal disturbance, although this is does not appear to be dose related [33]. The observed safe level (OSL) risk assessment method has indicated that the evidence of safety for CoQ10 is very strong at doses of up to 1200 mg/day, although much higher levels have been used in some randomised controlled trials without adverse effects. Supplementation with CoQ10 does not appear to affect the biosynthesis of endogenous CoQ10 [33].

**Importance of CoQ10 supplement formulation**

Bioavailability is defined as the proportion of an ingested substance that is absorbable from the digestive tract into the bloodstream. The bioavailability of CoQ10 is low, typically of the order of 5%; this is a consequence of its chemical structure, i.e., it is a lipid soluble molecule consisting of a benzoquinone ring and a side chain comprising ten isoprenoid units. The bioavailability of CoQ10 is in turn subject to the formulation of the supplement [34]. Supplemental CoQ10 is manufactured via a procedure in which CoQ10 crystals in polymorphic form are obtained as an end product of a yeast fermentation process. Since the human digestive tract is not capable of absorbing CoQ10 in polymorphic crystalline form, it is important that supplements are formulated such that the CoQ10 polymorphic crystals are transformed (via a thermal recrystalisation process) into an acicular form, which in turn is more readily dispersed into single CoQ10 molecules in the digestive tract for subsequent absorption. In the absence of such crystal transformation, the bioavailability of supplemental CoQ10 in


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normal subjects is reduced by 75% [34]. In addition, because food supplements are not subject to the same strict quality standards as prescription-type medicines, it is important that CoQ10 supplements should be manufactured to pharmaceutical standards if they are to be used in clinical studies; furthermore, such CoQ10 supplements should be of proven bioavailability in human subjects, as documented in the peer-reviewed medical literature. In this regard, to date there is only one CoQ10 product (Myoqinon) that has received a marketing authorisation within the EU, for the adjuvant treatment of heart failure.

## Conclusion

MSA is a progressive neurodegenerative disorder for which there is relatively little available in terms of conventional treatment. There is evidence from a number of clinical studies for a depletion of CoQ10 levels in relevant tissues from MSA patients (Figure 1), and there is a rationale for the involvement of CoQ10 in the pathogenesis of this disorder, based on its role in cellular energy metabolism, and its antioxidant and anti-inflammatory action.

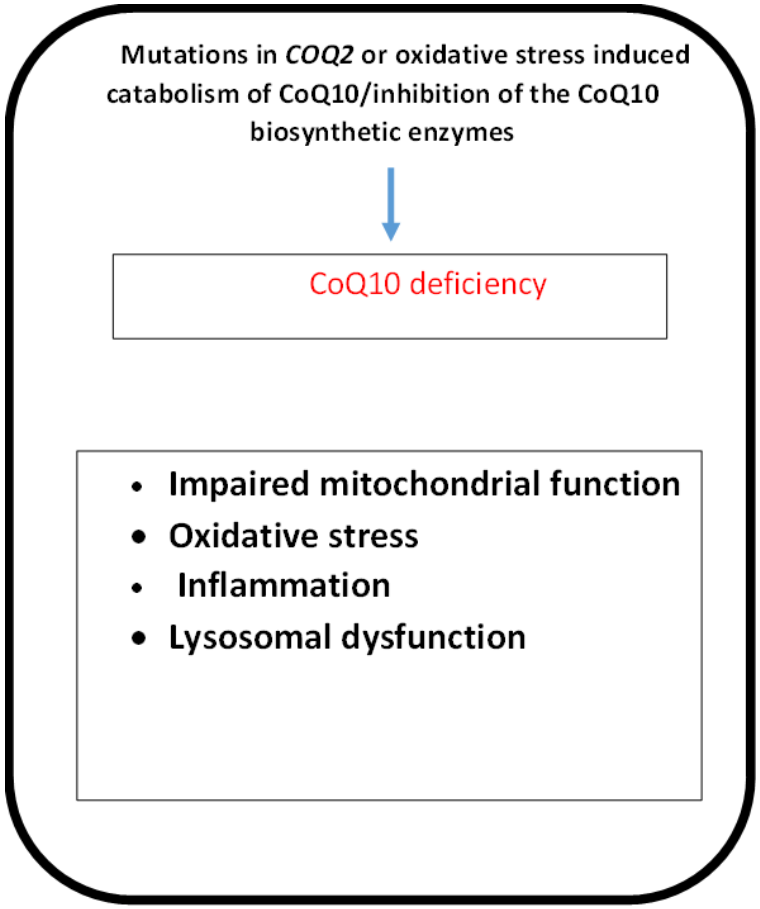


**Figure 1:** The potential causes of a CoQ10 deficiency in multiple system atrophy and its contribution to disease pathophysiology. COQ10: Coenzyme Q10.


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What is now required is a clinical study to investigate the potential benefit of supplementing CoQ10 in MSA patients. On the UMINCTR clinical trials registry, a randomised controlled study to investigate the efficacy of CoQ10 in MSA patients is listed as being underway (UMINooo031771), under the direction of Professor S. Tsuji of University of Tokyo Hospital, but no other information is currently available: (https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=Rooo036134)

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