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Coenzyme Q10 as a Peripheral Biomarker for Multiple System Atrophy

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Multiplesystematrophy(MSA) is a progressive disorder, characterized by cerebellar ataxia, parkinsonism, and autonomic dysfunction. Brains of patients with MSA show extensive glial cytoplasmic inclusions that contain α -synuclein in the oligodendrocytes as well as extensive neurodegeneration in the cerebellum and basal ganglia. The pathophysiologic mechanism of MSA is poorly understood; therefore, it has been difficult to develop effective therapy for this disorder.

Although MSA is predominantly sporadic, rare familial cases have been identified in Japan. Using whole-genome sequencing technology, *COQ2* mutations have been identified as a genetic cause for MSA in these families.¹ Heterozygous mutations of *COQ2*, in particular the V393A mutation, are genetic risk factors for sporadic MSA in Japan but not in Europe or North America. Follow-up studies confirmed the association of *COQ2* with MSA in a Taiwanese cohort and a Chinese cohort,^{2,3} but the association was not replicated in other studies from East Asia.^{4–6} Other European and North American studies also did not find the association between *COQ2* mutations and MSA.^{7,8} These data suggest that the association between *COQ2* mutation and MSA might be population-specific. A meta-analysis of East Asian cohorts (Japan, Taiwan, Korea, and China) supports the association of *COQ2* mutations and MSA.³ Indeed, patients with MSA in different geographic regions have diverse clinical presentations: Japanese patients have primarily the cerebellar subtype, whereas European patients have mostly the parkinsonism subtype. Consistent with this finding, *COQ2* mutations seem to be more common in patients with the cerebellar subtype of MSA.²

COQ2 encodes 4-para-hydroxybenzoate:polyprenyl transferase, the second enzyme in the biosynthetic pathway of co-enzyme Q10 (CoQ10),⁹ which is an electron carrier in the mitochondrial respiratory chain, and a potent antioxidant. Patients with MSA who have *COQ2* mutations have decreased levels of CoQ10 in their lymphoblastoid cells and postmortem brain tissues.¹ These molecular findings have revealed the importance of the CoQ10 biosynthetic pathway in MSA and raise the question: is CoQ10 deficiency also present in the brains of patients with sporadic MSA because of a shared disease mechanism between genetic and sporadic MSA? To address this issue, Schottlaender et al¹⁰ found that

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patients with sporadic MSA have decreased levels of CoQ10 in the cerebellum but normal levels in the frontal cortex when compared with controls. In addition, one study observed that patients with MSA without COQ2 mutations have 40% lower levels of CoQ10 in the cerebellum compared with controls, whereas the occipital cortex has normal levels of CoQ10.¹¹ These studies suggest that CoQ10 deficiency may play a role in sporadic MSA cases.

Thus, the identification of *COQ2* mutations and decreased levels of CoQ10 in patients with MSA has shed light on the pathologic mechanism underlying MSA. The cerebellum is the brain region with the lowest baseline levels of CoQ10,⁹ which may explain why cerebellar ataxia is the most common symptom in patients with primary or secondary CoQ10 deficiency, and why patients with MSA and COQ2 mutations manifest predominantly the cerebellar subtype. COQ2 mutations have been reported to cause childhood-onset cerebellar ataxia, retinopathy, encephalopathy, and nephropathy.⁹ Therefore, the rare patients with MSA and COQ2 mutations may be regarded as having an adult-onset variant of primary CoQ10 deficiency without prominent ophthalmologic or renal involvement. By contrast, individuals with sporadic MSA show a selective decrease of levels of CoQ10 in the cerebellum,^{10,11} potentially owing to environmental, genetic or epigenetic, and other factors influencing CoQ10 biosynthetic pathways. A study of enzyme levels in the CoQ10 biosynthetic pathways revealed that levels of PDSS1 and COQ5, but not other CoQ10-synthesizing enzymes, are selectively decreased in the cerebellum of patients with MSA.¹¹ To assess the consequences of CoQ10 deficiency, oxidative stress and mitochondrial respiratory chain enzymes activities were measured in the cerebellum of patients with MSA. A marker of lipid peroxidation, 4-hydroxynonenal, was increased in the cerebellum of patients with MSA, but CoQ10-dependent respiratory chain enzymes activities were normal, suggesting that the observed moderate deficiency of CoQ10 could gradually lead to oxidative damage during aging.¹¹ Additional questions about the role of CoQ10 deficiency in MSA need to be answered. For example, it is not clear how CoQ10 deficiency could contribute to α -synuclein accumulation in the oligodendrocytes, a pathologic hallmark of MSA. Deficiency of CoQ10 could affect α -synuclein homeostasis in the interface between the endoplasmic reticulum and mitochondrial interface, or it might interfere with neuron-to-oligodendrocyte spread of α -synuclein. Alternatively, CoQ10 deficiency could be part of a more general mitochondrial dysfunction caused by α -synuclein that eventually leads to neurodegeneration.

Another important question about CoQ10 deficiency in patients with MSA is whether it is present in the peripheral tissues of patients with MSA. And, if so, might it serve as a biomarker for MSA? In this issue of *JAMA Neurology*, Mitsui and colleagues¹² have addressed these issues by investigating plasma levels of CoQ10 in 44 patients with MSA and 39 controls. They found a 30% reduction of plasma levels of CoQ10 in patients with MSA. After controlling for *COQ2* genotypes, patients with MSA still had significantly lower levels of CoQ10, indicating that the lower plasma levels of CoQ10 in patients with MSA cannot be attributed to *COQ2* mutations.¹² In addition, patients with the cerebellar and parkinsonism subtypes of MSA had similarly decreased plasma levels of CoQ10. Consistent with these observations, Kasai et al¹³ found a decreased ratio of serum CoQ10 to cholesterol in patients with MSA.

Although measuring CoQ10 levels in plasma may be useful to monitor therapy and compliance, there are some limitations to measuring CoQ10 levels in plasma for diagnostic purposes. Because the biosynthetic pathway of CoQ10 is tightly linked to cholesterol homeostasis, blood levels of CoQ10 are affected by diet, hyperlipidemia, and hyperthyroidism, as well as by drugs (ie, statins). Furthermore, plasma levels of CoQ10 could be variable even in individuals with known mutations in genes encoding CoQ10-synthesizing enzymes, such as *COQ2* and *ADCK3*. Levels of CoQ10 in the muscles and fibroblasts provide a more reliable measurement.⁹

Although CoQ10 supplementation is an obvious and appealing therapeutic strategy for patients with MSA, CoQ10 and its derivatives have failed to show efficacy in several neurologic disorders, including Parkinson disease and Friedreich ataxia.^{14,15} In these disorders, mitochondrial functions are compromised; however, there is no evidence of CoQ10 deficiency, since levels of CoQ10 are normal in the brains of patients with Parkinson disease^{10,11} and in the cerebellum of patients with Friedreich ataxia.¹⁰ Mitochondria are responsible for many important biological functions; therefore, CoQ10 might not be able to rescue mitochondrial defects specific to Parkinson disease or Friedreich ataxia. On the other hand, the genetic evidence along with results of postmortem brain examinations and studies of peripheral blood biomarkers consistently indicate that CoQ10 might play a major role in MSA. Another possible cause for the lack of response to CoQ10 supplementation in Parkinson disease and Friedreich ataxia may be the low absorption and bioavailability that limit the increase of CoQ10 in cell mitochondria, where it is biologically active.⁹ This limitation is even more prominent in the brain because the exogenous CoQ10 must be able to cross the blood-brain barrier to effectively treat neurologic disorders; therefore, large doses of CoQ10 (approximately 1200-2400 mg/d) are generally needed to reach the brain.^{14,15} From the previous experience of clinical trials of CoQ10,¹⁴ these doses are generally well-tolerated. Moreover, efficacy of the therapy may be increased by the use of ubiquinol, the reduced form of CoQ10, which has greater bioavailability than CoQ10. Accordingly, a Japanese consortium led by Shoji Tsuji, MD, PhD, has initiated a safety and pharmacokinetic study on a reduced form of CoQ10 (MSA-01) in healthy individuals. The goal of the study is to investigate the CoQ10 concentration in plasma, leukocytes, and cerebrospinal fluid with different doses of MSA-01. Once the optimal dose has been determined, a randomized, double-blind, placebo-controlled clinical trial for MSA will soon be under way and plasma CoQ10 levels might serve as a biomarker to assess target engagement.

In conclusion, the recent discoveries of *COQ2* mutations in rare patients with MSA and of CoQ10 deficiency in the brain and blood of patients with MSA may lead to mechanism-based and rationale therapies for MSA, a rapidly progressive disorder in need of a disease-modifying therapy.

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