Coenzyme Q10 in Neuromuscular and Neurodegenerative Disorders

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Abstract: Coenzyme Q10 (CoQ10, or ubiquinone) is an electron carrier of the mitochondrial respiratory chain (electron transport chain) with antioxidant properties. In view of the involvement of CoQ10 in oxidative phosphorylation and cellular antioxidant protection a deficiency in this quinone would be expected to contribute to disease pathophysiology by causing a failure in energy metabolism and antioxidant status. Indeed, a deficit in CoQ10 status has been determined in a number of neuromuscular and neurodegenerative disorders.

Primary disorders of CoQ10 biosynthesis are potentially treatable conditions and therefore a high degree of clinical awareness about this condition is essential. A secondary loss of CoQ10 status following HMG-Coa reductase inhibitor (statins) treatment has been implicated in the pathophysiology of the myotoxicity associated with this pharmacotherapy.

CoQ10 and its analogue, idebenone, have been widely used in the treatment of neurodegenerative and neuromuscular disorders. These compounds could potentially play a role in the treatment of mitochondrial disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and other conditions which have been linked to mitochondrial dysfunction.

This article reviews the physiological roles of CoQ10, as well as the rationale and the role in clinical practice of CoQ10 supplementation in different neurological and muscular diseases, from primary CoQ10 deficiency to neurodegenerative disorders. We also briefly report a case of the myopathic form of CoQ10 deficiency.

Keywords: Coenzyme Q10, CoQ10 deficiency, idebenone, mitochondria, mitochondrial diseases, neurodegeneration, statins.

INTRODUCTION

Coenzyme Q10 (CoQ10), or ubiquinone, is an endogenously synthesized lipid, which shuttles electrons from complexes I (NDSH: Ubiquinone reductase) and II (succinate: ubiquinone reductase) and from the oxidation of fatty acids and branched-chain aminoacids (*via* flavin-linked dehydrogenases) to complex III (ubiquinol cytochrome c oxidase) of the mitochondrial respiratory chain (electron transport chain, ETC) [1] (Fig. **1**). The reduced form of CoQ10 known as ubiquinol also has antioxidant properties, protecting membrane lipids and proteins and mitochondrial deoxyribonucleic acid (mtDNA) against oxidative damage [1].

Intracellular synthesis is the major source of CoQ10, although a small proportion is acquired through diet (i.e. oily fish, organ meats such as liver, and whole grains). CoQ10 biosynthesis depends on the mevalonate pathway (Fig. **2**), a sequence of cellular reactions leading to farnesyl pyrophosphate, the common substrate for the synthesis of cholesterol, dolichol, dolichyl posphate, CoQ10, and for protein prenylation (a post-translational modification necessary for the targeting and function of many proteins) [1]. Cells synthesize CoQ10 *de novo*, starting with synthesis of the parahydroxybenzoate ring and the polyisoprenyl tail, which anchors CoQ10 to membranes [1] (Fig. **3**). The length of this tail varies among different organisms. In humans, the side chain is comprised of ten isoprenyls producing CoQ10 [1].

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In healthy individuals, oral administration of CoQ10 has been reported to improve subjective fatigue sensation and physical performance during fatigue-inducing workload trials [2].

CoQ10 has been widely used for the treatment of mitochondrial disorders (MD) and other neurodegenerative disorders, as well as its synthetic analogue, idebenone [3]. Potential treatment indications for the use of CoQ10 include migraine [4, 5], chronic tinnitus aurium [6], hypertension [7], heart failure and atherosclerosis [8], although the role of CoQ10 in such conditions is still an open question. CoQ10, which may ameliorate endothelial dysfunction [9], is an independent predictor of mortality in chronic heart failure, and there is a rationale for controlled intervention studies with CoQ10 in such condition [9, 10]. Although CoQ10 is also used for the prevention and treatment of cancer, there is as yet no convincing evidence of its efficacy treatment of this order [8].

No absolute contraindications are known for CoQ10, and adverse effects are rare [8]. Mild dose-related gastrointestinal discomfort is reported in <1% of patients [8]. Potential interactions with warfarin causing decreased international normalized ratio (INR) have been suggested [8]. Its various formulations demonstrate variation in bioavailability and dosage consistency, and there is a serious possibility that patients may have been treated suboptimally [8]. It is important to use brands that have passed independent testing for product purity and consistency [8]. During CoQ10 supplementation plasma CoQ10 levels should be monitored to ensure efficacy, given that there is variable bioavailability between commercial formulations, and known inter-individual variation in CoQ10 absorption [10]. However, plasma levels may not reflect that of the cell and other

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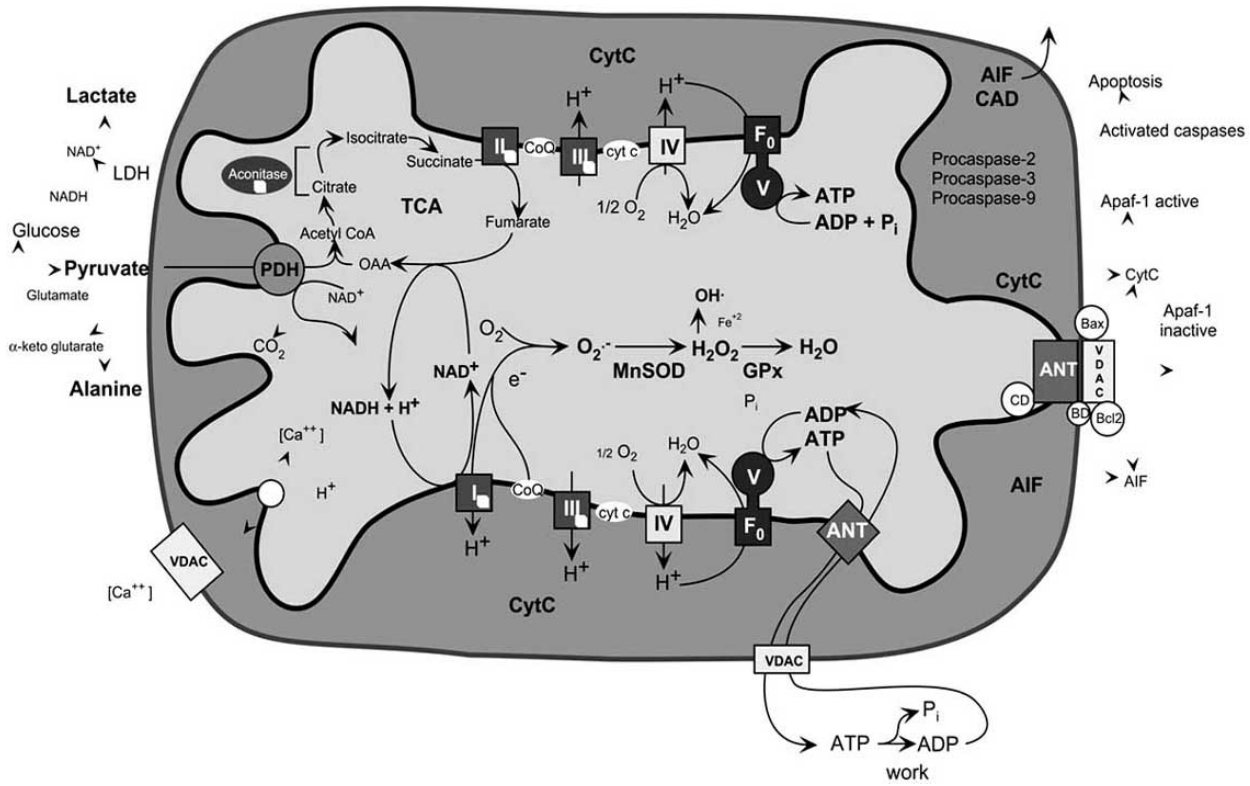

Fig. (1). Mitochondrial metabolism. Schematic representation of mitochondrial biochemical pathways, representing relationship between energy production (TCA and electron transport chain), reactive oxygen species production (superoxide $O2^{\cdot -}$, hydroxyl radical $OH^{\cdot}$), apoptosis regulation. Electron transport chain complexes: I (NADH:ubiquinone reductase), II (succinate:ubiquinone reductase), III (ubiquinone-cyt *c* oxidoreductase), IV (cytochrome *c* oxidase), F_0V (ATP synthase). ADP, adenosine 5'-diphosphate; ATP, adenosine 5'-triphosphate; AIF, apoptosis inducing factor; ANT, adenine nucleotide transporter; CAD, caspase-activated DNase; CytC, cytochrome *c*; GPX, glutathione peroxidase; LDH, lactic dehydrogenase; MnSOD, manganese superoxide dismutase; NAD+/NADH, oxidized/reduced nicotinamide adenine dinucleotide; OAA, oxalacetic acid; PDH, pyruvate dehydrogenase; Pi, inorganic phosphorus; TCA, tricarboxylic acid cycle; VDAC, voltage-dependent anion channel. From MITOMAP: A Human Mitochondrial Genome Database, allowed reproduction (http://www.mitomap.org).

surrogates such as blood mononuclear cells may be more appropriate [11].

MITOCHONDRIAL COMPARTMENT

Mitochondria are dynamic and pleomorphic organelles, which evolved from the aerobic bacteria which about 1.5 billion years ago populated primordial eukaryotic cells, thus endowing the host cells with oxidative metabolism (much more efficient than anaerobic glycolysis) [12]. Mitochondria are composed of a smooth outer membrane surrounding an inner membrane of significantly larger surface area that, in turn, surrounds a protein-rich core, the matrix [12]. They contain two to ten molecules of mtDNA [12]. In humans, the mtDNA is transmitted through maternal lineage [12].

The most crucial task of the mitochondrion is the generation of energy as adenosine triphosphate (ATP), by means of the ETC. The ETC is required for oxidative phosphorylation (which provides the cell with the most efficient energetic outcome in terms of ATP production), and consists of four multimeric protein complexes located in the inner mitochondrial membrane [12]. The ETC also requires the mobile electron carriers, cytochrome *c* (cyt *c*) and CoQ10. Electrons are transported along the complexes to molecular oxygen (O_2), finally producing water [12]. At the same time, protons are pumped across the mitochondrial inner membrane, from the matrix to the intermembrane space, by complexes I, III, and IV. This process creates an electrochemical proton gradient. ATP is produced by the influx of protons back through the complex V, or ATP synthase (the "rotary motor") [13]. This metabolic pathway is under control of both nuclear (nDNA) and mitochondrial genomes [12]. The human mtDNA encodes information for mitochondrial transfer RNAs (tRNAs), for ribosomal RNAs (rRNAs), and for 13 subunits of the ETC [12]. The remainder of the mitochondrial proteins are encoded by nDNA [12].

Mitochondria also play a central role in apoptotic cell death [see Fig. (**1**)] [14], and mitochondrial dysfunction appears to have a certain impact on the pathogenesis of several neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Azheimer's (AD) and Parkinson's disease (PD) [14]. Oxidative stress is an earlier event associated with mitochondrial dysfunction [14]. The transport of high-energy electrons through the mitochondrial ETC is a necessary step for ATP production, but it is also source of reactive oxygen species (ROS) production. The

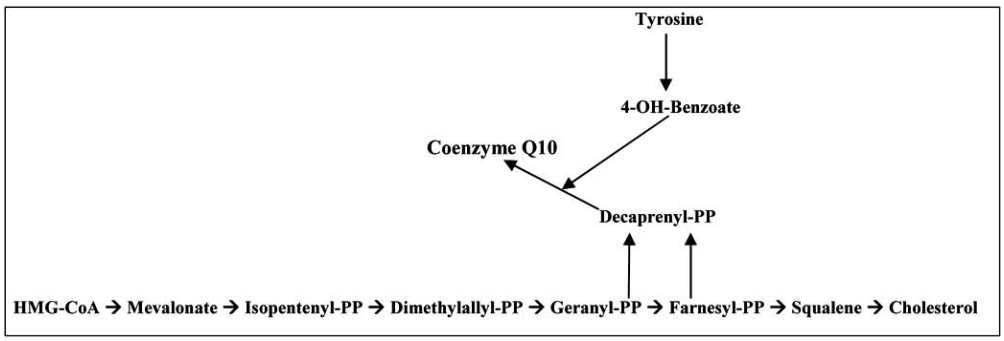

Fig. (2). A schematic representation of the mevalonate pathway, the sequence of cellular reactions that leads to farnesyl-PP. Farnesyl-PP is the common substrate for the synthesis of cholesterol, dolichol, and Coenzyme Q10, as well as for prenylation of proteins. Coenzyme Q10 contains also a benzoate ring originating from tyrosine. HMG-CoA reductase inhibitors, or statins, block production of mevalonate, a critical intermediary in the cholesterol synthesis pathway. A hypothesized mechanism of statin myopathy involve mitochondrial dysfunction caused by reduced intramuscular coenzyme Q10. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PP, pyrophosphate.

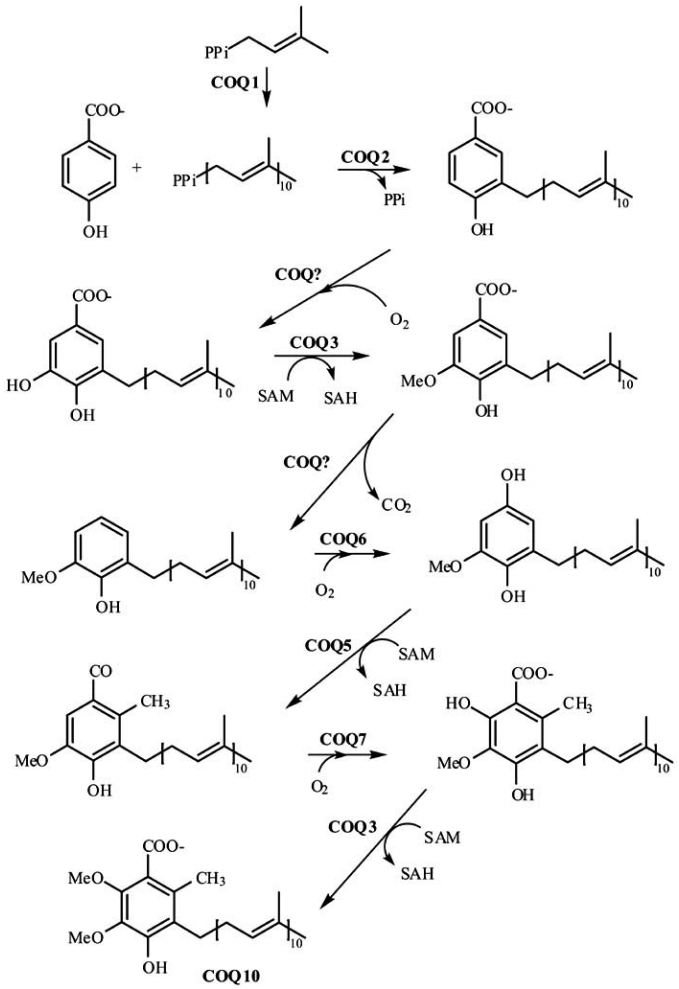

Fig. (3). Coenzyme Q10 biosynthesis. After 4-OH-benzoate and decaprenyl-PP [see Fig. (**1**)] are produced, at least seven enzymes (encoded by *COQ2-8* genes) catalyze condensation, methylation, decarboxylation, and hydroxylation reactions needed to synthesize Coenzyme Q10. Abnormalities in any part of the metabolic cascade will cause primary CoQ10 deficiency. From Mancuso M. *et al.*, Lett Drug Des Discov, 2006:3;378-82 (© 2006 Bentham Science Publishers Ltd.).

sites for ROS production in mitochondrial ETC are normally ascribed to the activity of complexes I and III [15] [see Fig. (**1**)]. At complexes I and III of the ETC, the high -energy electrons can react with O_2 to form superoxide ($O_2^{\cdot -}$) [16]. CoQ10 has also been reported to be a source of $O_2^{\cdot -}$ radical generation [14]. Up to 4-5% of the O_2 consumed by healthy mitochondria is thought to be converted into $O_2^{\cdot -}$, and this amount is higher in damaged and aged mitochondria [16]. When the respiratory system is inhibited, electrons accumulate in the early stages of the ETC (complex I and

CoQ10), where they are donated directly to O_2 to produce $O_2^{\cdot -}$ [16] [see Fig. (**1**)]. Conversely, the ETC is not universally accepted as the major site for mitochondrial ROS generation [17]. Studies have indicated that monoamine oxidases and $p66^{(Shc)}$, may contribute to the preponderance of mitochondrial ROS generation [18].

The accumulation of ROS can potentially damage biomolecules, including lipids, proteins and nucleic acids [14]. The accumulation of nDNA and mtDNA oxidative damage is thought to be deleterious in post-mitotic cells such as neurons, where DNA cannot be replaced through a cellu-lar division mechanism [14]. Indeed, oxidative base modifications to mtDNA could potentially cause bioenergetic dysfunctions resulting in cell death [14]. The cells possess an intricate network of defence mechanisms (mitochondrial manganese superoxide dismutase, glutathione peroxidase and other molecules) to neutralize excessive accumulation of ROS and, under physiological conditions, are able to cope with the flux of ROS [14]. Oxidative stress describes a condition in which cellular antioxidant defences are insufficient to keep the levels of ROS below a toxic threshold [14].

The mtDNA is particularly sensitive to oxidative damage because of its proximity to the inner mitochondrial membrane, where oxidants are formed, and because it is not protected by histones and is inefficiently repaired [14]. Because several of the mtDNA genes encode for subunits of the mitochondrial ETC, oxidative mtDNA damage, if not correctly repaired, could result in mutations and deletions in these genes which may therefore result in defective ETC complex enzymes being encoded. This may then result in mitochondrial dysfunction, increased production of ROS, and cellular death [14].

IN VITRO TESTS AND ANIMAL STUDIES

Several studies have investigated the role of CoQ10 as a neuroprotective agent *versus* ROS damage and apoptotic cell death. CoQ10 may act by stabilizing the mitochondrial membrane when neuronal cells are subjected to oxidative stress [19]. Pre-treatment with water-soluble CoQ10 maintained mitochondrial membrane potential during oxidative stress and reduced the amount of mitochondrial ROS generation [19]. The evidence of mitochondrial involvement in neurodegenerative diseases [14] allowed the hypothesis that CoQ10 may have a protective role in such diseases. Complex I dysfunction has been implicated in the pathogenesis of PD [14]. Rotenone, an insecticide which is a specific inhibitor of complex I, produced selective damage in the striatum and the globus pallidus, but the substantia nigra was spared [20]. Winkler-Stuck and co-workers [21] observed that the activity of ETC complexes, which were impaired in skin fibroblasts from a subgroup of PD patients, was restored after cultivation in the presence of 5 μM CoQ10. The neuroprotective role of CoQ10 has been also studied in other cellular models of PD, such as iron-induced apoptosis in cultured human dopaminergic neurons [22]. Iron-induced damage is mediated by ROS production and apoptosis activation; CoQ10 attenuated such iron-induced cellular damage [22]. Recently, CoQ10 has been found to be effective in a PD mouse model of MPTP toxicity, reversing dopamine depletion, loss of tyrosine hydroxylase neurons and induction of alpha-synuclein inclusions in the substantia nigra pars compacta [23]. However, the positive effect of CoQ10 on PD patients has not been clearly demonstrated in clinical trials (see "Coenzyme Q10 and neurodegenerative disorders").

Increasing evidence suggests that AD is associated with oxidative damage and mitochondrial dysfunction [14, 24]. Exogenous CoQ10 was found to protect neuroblastoma cells from β-amyloid neurotoxic effect; dietary supplementation of CoQ10 to AD mice suppressed brain protein carbonyl levels, which are markers of oxidative damage [14]. This suggests that oral CoQ10 may be a viable antioxidant strategy for neurodegenerative disease [24]. The efficacy of CoQ10 treatment against β-amyloid induced mitochondrial dysfunction has been evaluated also in brains of diabetic rats, where CoQ10 treatment was found to attenuate the decrease in oxidative phosphorylation and avoided the increase in hydrogen peroxide production induced by the neurotoxic peptide [25]. An *in vivo* volume MRI study on mice with mutation in the amyloid precursor protein showed that CoQ10 significantly delayed hemispheric and hippocampal atrophy [26]. Furthermore, the efficacy of CoQ10 as a neuroprotective factor against cognitive impairment has been evaluated in mice with reduced cognitive performance [27]. In aged mice CoQ10, combined with alpha-tocopherol, could have a role in improving learning [28].

In a mouse model of Huntington's Disease (HD) *in vivo* phosphorus magnetic resonance spectroscopy (31P-MRS) has been used in order to evaluate the antioxidant effect of CoQ10 and vitamin E on the activity of creatine kinase (CK), a sensitive indicator of brain energy metabolism dysfunction [29]. The results showed that CoQ10 and vitamin E prevented the increase of CK and the decrease of CoQ10 content in brain tissue, but were ineffective to prevent the decline of ETC function [29]. Smith and co-workers [30] reported a dose dependent therapeutic benefit when CoQ10 was administered to the mouse model of HD, improving motor performance, grip strength, reducing weight loss, brain atrophy and huntingtin inclusions [30]. Combined minocycline (an antibiotic with anti-apoptotic and neuroprotective properties [31]) and CoQ10 therapy in a mouse model of HD ameliorated behavioral and neuropathological alterations, reduced gross brain atrophy, striatal neuron atrophy, and huntingtin aggregation, and significantly extended survival and improved motor performance to a greater degree than either minocycline or CoQ10 alone [32].

The antioxidant function of CoQ10 has been also studied in noise-induced hearing loss (NIHL) [33, 34]. The administration of a water-soluble CoQ10 formulation to a guinea pig model of acoustic trauma prevented apoptosis and improved hearing [33].

COENZYME Q10 PRIMARY DEFICIENCY

There is a strong rationale for using CoQ10 supplementation to treat patients with primary CoQ10 deficiency [35, 36].

Primary CoQ10 deficiency is an uncommon heterogeneous condition which has been associated with five major known syndromes: (i) encephalomyopathy (with recurrent

myoglobinuria, brain involvement and ragged red fibers); (ii) severe infantile multisystemic disease; (iii) cerebellar ataxia; (iv) Leigh syndrome (growth retardation, ataxia and deafness); (v) isolated myopathy [35]. Primary CoQ10 deficiencies due to mutations in ubiquinone biosynthetic genes (i.e. *COQ2*, *PDSS1*, *PDSS2*, *CABC1*) have been identified in patients with the infantile multisystemic and cerebellar ataxic phenotypes [36]. In contrast, secondary CoQ10 deficiencies, due to mutations in genes not directly related to ubiquinone biosynthesis (i.e. *APTX*, *ETFDH*, *BRAF*) [36, 37], have been identified in patients with cerebellar ataxia, pure myopathy, and cardiofaciocutaneous syndrome [36].

The myopathic form of CoQ10 deficiency is potentially treatable (see below). The only current available CoQ10 deficiency treatments is CoQ10 supplementation. Therefore, a correct and timely diagnosis is crucial.

Case Report

A 26-year-old man came to our attention for mildly increased blood CK levels (ranging from 300 to 500 U/L [normal <180]), exercise intolerance and two episodes of myoglobinuria**.** There was no family history of neurological or muscular disorders. Motor and intellectual milestones were regular**.** At physical examination, there was not muscular weakness. Blood lactate levels at rest and during exercise were normal, as well as electromyography and nerve conduction studies. 31P-MRS muscular metabolic profile was similar to normal subjects. Muscular biopsy showed mild myopathic signs. Cytochrome *c* oxidase (COX) staining showed isolated hyporeactive fibers, with peripheral rims, but not clear signs of mitochondrial dysfunction (COX-deficient fibers). SDH (succinate dehydrogenase, ETC complex II) and NADH staining were also present with rare peripheral rims. Muscle immunohistochemistry for dystrophine, dysferlin, alfa-sarcoglycan, laminine and emerine was normal. DNA analysis for dystrophin gene was negative. The mitochondrial ETC activities in muscle were also normal. CoQ10 concentration was determined in a skeletal muscle specimen by a high-performance liquid chromatography method with ultraviolet detection (275 nm), using the Coenzyme Q10 Kit (Chromsystems) [37]. On analysis the patients skeletal muscle was found to have a CoQ10 level 54% of the reference mean value. Therefore, the patient started substitutive therapy at an initial dose of 50 mg x 3/day, gradually increased up to 500 mg x 3/day, with a dramatic improvement of the exercise intolerance. CK levels remained mildly increased, but no further episodes of myoglobinuria have so far been reported.

The myopathic form of CoQ10 deficiency is a rare disease characterized by subacute (3-6 months) onset of exercise intolerance and proximal limb weakness without central nervous system involvement, increased serum lactate and CK levels. Frequently it is associated with lipid droplets with subtle signs of mitochondrial dysfunction at skeletal muscle level, and reduced complexes I+III (NADH: cytochrome c reductase) and II+III (Succinate: cytochrome c reductase) activities (both complexes I+III and II+III rely on endogenous CoQ10 for activity), and good clinical response to CoQ10 supplementation [35, 38]. Our patient did not present biochemical mitochondrial ETC defects, nor lipid storage, but clinically improved after a period of oral CoQ10 intake. CoQ10 deficiency is an autosomal recessive mitochondrial disorder but a dominant effect cannot be discarded. Infantile mitochondrial encephalomyopathy has been associated to mutations in the first and second subunits of decaprenyl diphosphate synthase (*PDSS1* and *PDSS2*), in the mevalonate pathway [39, 40]. Mutations in *PDSS1* seem to lead to a milder phenotype than mutations in *PDSS2* in the limited number of patients assessed. Patients with mutations in para-hydroxybenzoate-polyprenyl transferase (*COQ2*), a component of the CoQ10 biosynthesis complex that modifies the ring, share early-onset nephrosis and encephalophaty [40, 41]. A myopathic form of CoQ10 deficiency has been reported to occur as the result of a mutation in the electron-transferring-flavoprotein dehydrogenase (*ETFDH*) gene [37]. *ETFDH* is also linked to another metabolic disorder, glutaric aciduria type II (GAII) [37]. Myopathic CoQ10 deficiency with pathogenic *ETFDH* mutations and late-onset GAII probably are the same disease [37]. As CoQ10 is the direct acceptor of electrons from the electron-transferring-flavoprotein, the lack of the reducing enzyme may downregulate the synthesis of CoQ10 [37]. Alternatively, faulty binding of the enzyme to CoQ10 could result in excessive degradation of the acceptor molecule [37]. Since CoQ10 deficiency/late-onset GAII is treatable, the diagnosis should be considered both in children and in adults with high-serum CK, proximal myopathy (with or without hepatopathy or encephalopathy), multiple acyl-CoA deficiency, lipid storage myopathy and decreased activity of ETC complexes I, II + III and IV [37]. It has been suggested that patients should be treated with both CoQ10 and riboflavin [37].

Interestingly, some cases of the ataxic variant of CoQ10 deficiency have been linked to a homozygous mutation in the aprataxin (*APTX*) gene, which causes ataxia oculomotor apraxia type 1 [42, 43]. The relationship beetween this protein, involved in DNA repair, and CoQ10 homeostasis is still unclear [42, 43]. CoQ10 deficiency with cerebellar ataxia has been associated to mutation in *CABC1*/*COQ8* gene [44] which encodes the Abc1 protein kinase *ADCK3* [45]. Very recently, a patient with primary CoQ10 deficiency whose clinical history started with neonatal lactic acidosis and who later developed multisytem disease including intractable seizures, global developmental delay, hypertrophic cardiomyopathy, and renal tubular dysfunction was reported to harbour a homozygous stop mutation affecting a highly conserved residue of *COQ9* gene, leading to the truncation of 75 amino acids [46].

CoQ10 deficiency is a treatable condition, so a high grade of "clinical suspicion" about this diagnosis is essential, especially for paediatricians and infantile neurologists. An early treatment with high-dose CoQ10 might radically change the natural history of this group of diseases [35, 47, 48]. Patients with all forms of CoQ10 deficiency have shown clinical improvement with oral CoQ10 supplementation, but cerebral symptoms are only partially ameliorated (probably because of irreversible structural brain damage before treatment and because of poor penetration of CoQ10 across the blood-brain barrier) [49]. Patients were given various doses of CoQ10 ranging from 90 to 2000 mg daily. The small number of patients precluded any statistical analysis but improvement was undoubtedly reported [35, 49]. In several patients CoQ10 supplementation also ameliorated the mitochondrial function (ETC activities, lactic acid values,

muscle CoQ10 content) [49]. The beneficial effects of exogenous CoQ10 require high doses and long-term administration. Also patients with ataxia oculomotor apraxia type 1 may benefit from this treatment [35].

ROLE OF COQ10 IN OTHER MITOCHONDRIAL DISORDERS

MD are commonly defined as a group of disorders caused by impairment of the mitochondrial ETC [12], which does not include other defects of mitochondrial metabolism such as pyruvate dehydrogenase deficiency, carnitine deficiency or fatty acid oxidation defects. The effects of mutations which affect the ETC may be multisystemic, with involvement of visual and auditory pathways, heart, central nervous system, and skeletal muscle [12]. The estimated prevalence of MD is 1-2 in 10000 [50]. MD are, therefore, one of the commonest inherited neuromuscular disorders.

The genetic classification of MD distinguishes disorders due to defects in mtDNA from those due to defects in nDNA [12] (Table **1**). The first ones are inherited according to the rules of mitochondrial genetics (maternal inheritance, heteroplasmy and the threshold effect, mitotic segregation) [12]. Each cell contains multiple copies of mtDNA (polyplasmy), which in normal individuals are identical to one another (homoplasmy) [12]. Heteroplasmy refers to the coexistence of two populations of mtDNA, normal and mutated. Mutated mtDNA in a given tissue have to reach a minimum critical number before oxidative metabolism is impaired severely enough to cause dysfunction (threshold effect) [12]. Differences in mutational loads surpassing the pathogenic threshold in some tissues but not in others may contribute to the heterogeneity of phenotypes. Because of the mitotic segregation, the mutation load can change from one cell generation to the next and, with time, it can either surpass or fall below the pathogenic threshold [12]. Further, the pathogenic threshold varies from tissue to tissue according to the relative dependence of each tissue on oxidative metabolism [12]. For instance, central nervous system, skeletal muscle, heart, endocrine glands, the retina, the renal tubule and the auditory sensory cells are highly dependent on oxidative metabolism for energy generation.

MD related to nDNA are caused by mutations in structural components or ancillary proteins of the ETC, by

Table 1. Genetic Classification of Well Characterized Mitochondrial Diseases (MD). ETC, Electron Transport Chain; MELAS, Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes; MERRF, Myoclonic Epilepsy with Ragged red Fibers; MNGIE, Mitochondrial Neurogastrointestinal Encephalomyopathy; MLASA, Mitochondrial Myopathy and Sideroblastic Anemia; NARP, Neuropathy, Ataxia, Retinitis Pigmentosa; PEO, Progressive external Ophthalmoplegia

Disorders of mitochondrial genome	MD caused by nuclear gene defects
Sporadic rearrangements	**Defects of genes encoding for structural proteins of the complexes of ETC**
Kearns-Sayre syndrome (KSS)	Leigh Syndrome
Pearson syndrome	Cardiomyopathy hypertrophic, histiocitoide
Sporadic PEO	Paraganglioma, pheochromocytomas
Diabetes and deafness	Multisystemic syndromes
Sporadic point mutations	**Defects of genes encoding factors involved in the assembling complexes of ETC ("Assembly genes")**
PEO	Leigh Syndrome
MELAS	Multisystemic Syndromes
Exercise intolerance	**Defects of genes altering mtDNA stability and integrity (intergenomic communication)**
Isolated myopathy	Autosomal PEO
Maternal-inherited mtDNA point mutations	Early-onset parkinsonism
Genes encoding structural proteins	Multisystemic syndromes
Leber hereditary optic neuropathy (LHON)	MNGIE
NARP	mtDNA depletion syndromes
Maternal-inherited Leigh syndrome	**Coenzyme Q10 deficiency**
Genes encoding tRNAs	Cerebellar form *coq2*, *coq8*
MELAS	Myopathic form *etfdh*
MERRF	Encephalomyopathy
Cardiomyopathy and myopathy (MIMyCa)	Infantile multisystemic disease *pdss1*, *coq2*
PEO	Leigh syndrome *pdss2*
Isolated myopathy	**Defects of the lipid milieu**
Diabetes and deafness	Barth syndrome
Sensorineural hearing loss	**Syndromes due to defects of mitochondrial ribonucleic acid**
Hypertrophic cardiomyopathy	MLASA
Tubulopathy	**Defects of mitochondrial fission or fusion**
Genes encoding rRNAs	Autosomal dominant optic atrophy (ADOA) Charcot-Marie-Tooth (CMT) 2A
Aminoglycosides-induced deafness	
Hypertrophic cardiomyopathy	

defects of the membrane lipid milieu, of CoQ10 biosynthetic genes (see "Coenzyme Q10 primary deficiency") and by defects in intergenomic signalling (associated to mtDNA depletion or multiple deletions) [12]. Moreover, the occurrence of a single large-scale deletion, common cause of progressive external ophthalmoplegia (PEO), is almost sporadic [12].

In MD patient muscle homogenates, significantly positive correlation was observed between complexes I + III and II + III activities with CoQ10 concentration [51]. Recently, CoQ10 content and ETC enzyme analysis were determined in muscle biopsy specimens of 82 children with suspected mitochondrial myopathy [52]. Muscle total, oxidized, and reduced CoQ10 concentrations were significantly decreased in the probable defect group [52]. Total muscle CoQ10 was the best predictor of an ETC complex abnormality [52]. Determination of muscle CoQ10 deficiency in children with suspected MD may facilitate diagnosis and encourage earlier supplementation of this agent [52].

Therapy of MD is still inadequate, despite great progress in the molecular understanding of these disorders [3]. Apart from symptomatic therapy, administration of metabolites and cofactors, including CoQ10, as well as of ROS scavengers, is the mainstay of real-life therapy. On the other hand, there is currently no clear evidence supporting the use of any intervention in MD [53], and further research is needed. There have been very few randomised controlled clinical trials for the treatment of MD. Those that have been performed were short, and involved fewer than 20 study participants with heterogeneous phenotypes [53].

The multitude of generally positive anecdotal data together with the lack of negative side effects has contributed to the widespread use of CoQ10 in MD [54, 55]. In studies with eight to 44 patients CoQ10 seemed to demonstrate positive trends in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS), Kearns-Sayre syndrome (KSS), and myoclonus epilepsy with ragged red fibers (MERRF) [8]. Chen and co-workers [56] performed a randomised, double-blind cross-over trial on eight MD patients. Both subjective and objective measures showed a trend towards improvement on treatment, but the global Medical Research Council (MRC) index score of muscular strength was the only measure reaching statistical significance [56]. However, there is a need for controlled trials in large cohorts of patients [53].

Recently, Rodriguez and co-workers [57] studied the effect of a combination therapy (creatine, CoQ10, and lipoic acid) on several outcome variables using a randomized, double-blind, placebo-controlled, crossover study design in seventeen patients with various MD. Lipoic acid is found naturally within the mitochondria and is an essential cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and is also a potent antioxidant [57]. Such combination therapy resulted in lower resting plasma lactate and a lowering of oxidative stress as reflected by a significant reduction in urinary 8-isoprostanes and a directional trend in 8-hydroxy-2'-deoxyguanosine (8-OHdG) excretion [57]. Isoprostanes are prostaglandin-like compounds formed by the peroxidation of arachadonic acid, and are considered one of the most reliable markers to assess oxidative stress *in vivo* [58]. 8-OHdG is formed by the hydroxylation of guanosine residues and is often used as a biomarker of oxidative damage to DNA [59]. Further, the combination therapy attenuated the decrease in peak ankle dorsiflexion strength that was observed following the placebo phase [57].

Two methodologies useful to detect the overall level of oxidative damage in MD patients are micronucleus assay followed by fluorescence in situ hybridisation (FISH), and comet assay in cultured lymphocytes [60]. An increased frequency of micronucleated cells is considered a good marker of genotoxic effects [60]. The single cell gel electrophoresis (comet) assay in lymphocytes can estimate levels of primary and oxidative DNA damage in the body [61]. A group of MD patients showed an increased level of chromosome damage, expressed as frequency of micronucleated lymphocytes, in comparison with healthy individuals [62]. Patients receiving a two week therapy with CoQ10 showed a statistically significant reduction in the frequency of micronucleated cells after therapy [62]. Therefore, the DNA damage in MD patients was decreased by CoQ10, which is also an efficient antioxidant [62].

Idebenone has been reported to improve brain and skeletal muscle metabolism in isolated cases of MD, and seemed to enhance the rate and degree of visual recovery in Leber Hereditary Optic Neuropathy [53]. Leber's disease is a maternally inherited condition characterized by acute or subacute bilateral loss of vision, usually in young individuals [12]. Several point mutations in the mitochondrial genome have been identified in patients with the condition [12].

Therapy for MD remains inadequate and mostly symptomatic, but the rapidly increasing knowledge of their molecular defects and pathogenic mechanisms allows for some cautious optimism about the development of effective treatments in the next future [12]. One of the "cocktails" of choice for the treatment of MD may be a combination of L-carnitine (1,000 mg three times a day) and CoQ10 (at least 300 mg a day), with the rationale of restoring free carnitine levels and exploiting the oxygen radical scavenger properties of CoQ10 [12].

COENZYME Q10 AND STATINS

Statins are currently the most effective medications for reducing low-density lipoprotein (LDL) cholesterol concentrations [63]. Statins competitively inhibit HMG-CoA reductase thereby decreasing synthesis of mevalonate, a critical intermediary in the cholesterol synthesis pathway [see Fig. (**2**)] [63]. Although generally safe, they have been associated with a variety of myopathic complaints. Their most serious and frequent side effects are a variety of myopathic complaints ranging from mild myalgia to fatal rhabdomyolysis [63]. Statins *via* inhibition HMG-CoA reductase cause a decrease in the synthesis of farnesyl pyrophosphate, an intermediate in the synthesis of CoQ10 [63].

The fact that statins block the mevalonate pathway has prompted the idea that statin-induced CoQ10 deficiency may be involved in the pathogenesis of statin myopathy (the primary adverse effect limiting their use) [63]. Thus, supplementing with CoQ10 may be recommended to prevent the myopathic side effects associated with the statins. Evidences for or against this hypothesis have been reviewed by Marcoff

and Thompson [63], but the question remains to be answered. A study performed on a sample of muscle biopsy of patients with statin drug-related myopathy showed that the decrease of CoQ10 concentration in muscle did not cause histochemical or biochemical evidence of mitochondrial myopathy or morphologic evidence of apoptosis in most patients [64].

A study designed to assess the effect of high-dose statin treatment has been performed on 48 patients with hypercholesterolemia, randomly assigned to receive simvastatin, atorvastatin, or placebo for 8 weeks [65]. Muscle ubiquinone concentration was reduced significantly in the simvastatin group, but no reduction was observed in the atorvastatin or placebo group [65]. Also ETC and citrate synthase activities were reduced in patients taking simvastatin [65].

The effect of simvastatin on CoQ10 plasmatic levels has been compared with the effect of ezetimibe (a cholesterol absorption inhibitor) and of the coadministration simvastatin/ezetimibe [66]. While simvastatin and the combination of simvastatin and ezetimibe significantly decreased plasma CoQ10 levels, ezetimibe monotherapy did not [66].

A randomized double-blind, placebo-controlled study that examined the effects of CoQ10 and placebo in hypercholesterolemic patients treated by atorvastatin showed a similar decrease in LDL carriers in the two groups and an high increase of CoQ10 levels in the CoQ10 group [67]. In particular, the placebo group showed a mean reductions of plasma CoQ10 levels by 42%, whereas patients supplemented with CoQ10 showed a mean increase in plasma CoQ10 by 127% [67]. However, these changes in plasma CoQ10 levels showed no relation to the changes in serum transaminase and CK levels [67]. Further studies are needed in order to evaluate the role of CoQ10 supplementation during statin therapy [63].

COENZYME Q10 AND NEURODEGENERATIVE DISORDERS

There is increasing evidence that impairment of mitochondrial function and oxidative damage are contributing factors to the pathophysiology of Parkinson's Disease (PD), and a recent study reported a deficit in brain CoQ10 levels in PD patients, which may be involved in the pathophysiology of PD [68]. In PD patients, CoQ10 was well tolerated at doses as high as 1200 mg daily [69]. A study on 130 PD patients without motor fluctuations and a stable antiparkinsonian treatment reported that nanoparticular CoQ10 (300 mg daily) was safe and well tolerated, and led to plasma levels similar to 1200 mg/day of standard formulations, although did not result in symptomatic effects in midstage PD [70]. The efficacy of CoQ10 in PD remains an open question [71].

A very recent short-term, randomized, placebo-controlled trial was performed in progressive supranuclear palsy (PSP). PSP, the second most common cause of parkinsonism after PD, is characterized by down gaze palsy with progressive rigidity and imbalance leading to falls. Impairment of mitochondrial ETC complex I activity has been reported in PSP [72]. CoQ10 improved cerebral energy metabolism on magnetic resonance spectroscopy studies [72]. Clinically, PSP patients improved slightly, but statistically significantly, upon CoQ10 treatment compared to placebo [72].

In HD, CoQ10 may slow the decline in total functional capacity over 30 months [73]. HD is a genetic disease characterized by psychiatric disturbances, progressive cognitive impairment, choreiform movements, and death 15 to 20 years after the onset of symptoms. Various lines of evidence demonstrated the involvement of mitochondrial dysfunction in the pathogenesis of HD, but the precise role of mitochondria in the neurodegenerative cascade leading to HD is still unclear. Kieburtz and co-workers [73] carried out a trial in which 347 patients with early HD were randomized to receive CoQ10 300 mg twice daily, remacemide hydrochloride 200 mg three times daily, both, or neither treatment, and were followed every 4 to 5 months for a total of 30 months. Patients treated with CoQ10 showed a trend toward slowing the decline in total functional capacity decline over 30 months, as well as beneficial trends in some secondary measures [73]. CoQ10 was well tolerated by HD patients.

Moreover, no reported side effects have been reported in 31 subjects with Amyotrophic Lateral Sclerosis (ALS) treated with doses of CoQ10 as high as 3,000 mg/day for 8 months [74]. ALS is a motor neuron disease, with selective degeneration of the anterior horn cells of the spinal cord and cortical motor neurons. Approximately 90% of cases are sporadic, and 10% are familial. About 20% of familial cases result from mutation in the gene encoding for the Cu/Zn-superoxide dismutase (*SOD1*). The aetiology and pathogenesis of the sporadic form of the disease are poorly understood; mitochondrial dysfunction and oxidative stress are involved [14]. Mice expressing mutant *SOD1* provide an animal model of ALS. A significant increase in the oxidized form of CoQ10 and in the ratio of oxidized form of CoQ10 to total CoQ10 have been reported in 20 sporadic ALS patients [75]. Moreover, the latter parameter significantly correlated with the duration of disease, supporting systemic oxidative stress in the pathogenesis of sporadic ALS [75]. However, a recent US randomized, controlled phase II trial has demonstrated that CoQ10 administration in ALS patients did not appear to slow the progression of this disease [76].

Most trials have demonstrated that idebenone (5 mg/kg daily) reduced cardiac hypertrophy in Friedreich's ataxia [77, 78]. Friedreich's ataxia is the most common hereditary ataxia among white people, and it is caused by a trinucleotide expansion in the *X25* gene. In this disorder, the genetic abnormality results in the deficiency of frataxin, a protein targeted to the mitochondrion [78]. Although the exact physiological function of frataxin is not known, its involvement in iron–sulphur cluster biogenesis has been suggested [78]. A possible manifestation of this disease is cardiomyopathy. A recent pilot study investigated the potential for high dose CoQ10/vitamin E therapy to modify clinical progression in Friedreich's ataxia [79]. Fifty patients were randomly divided into high or low dose CoQ10/vitamin E groups [79]. At baseline serum CoQ10 and vitamin E levels were significantly decreased in patients [79]. During the trial CoQ10 and vitamin E levels significantly increased in both groups [79]. Serum CoQ10 levels have been reported to be the best predictor of a positive clinical response to CoQ10/vitamin E therapy [79] in this condition. Recently, a randomised, placebo-controlled trial has been conducted on

48 patients with genetically confirmed Friedreich's ataxia [80]. Treatment with higher doses of idebenone was generally well tolerated and associated with improvement also in neurological function and activities of daily living in patients with Friedreich's ataxia [80]. The degree of improvement correlated with the dose of idebenone, suggesting that higher doses may be necessary to have a beneficial effect on neurological function [80].

The role of mitochondrial dysfunction and oxidative stress in the pathogenesis of neurodegenerative diseases is well documented [14]. It will be important to develop a better understanding of the role of oxidative stress and mitochondrial energy metabolism in neurodegeneration, since it may lead to the development of more effective treatment strategies for these devastating disorders.

CONCLUSION

In addition to primary CoQ10 deficiency, CoQ10 treatment has been reported to elicit some efficacy in the treatment of MD and neurological disorders not directly linked to a primary deficiency in this quinone. The reason for this efficacy are uncertain but may be the ability of this quinone to increase cellular antioxidant status or enhance mitochondrial ETC function. CoQ10 therapy has been shown to be relatively safe with few adverse effects being reported. Additional studies on the potential usefulness of CoQ10 supplementation as an adjunct to conventional therapy in neurological diseases, particularly neurodegenerative, are still required before this quinine can be accepted as a legitimate and universally accepted treatment for these disorders.

ABBREVIATIONS

31P-MRS = Phosphorus magnetic resonance spectroscopy

AD = Alzheimer's disease

ALS = Amyotrophic lateral sclerosis

ATP = Adenosine triphosphate

CK = Creatine kinase

CoQ10 = Coenzyme Q10

cyt *c* = Cytocrome *c*

ETC = Electron transport chain

HD = Huntington's disease

KSS = Kearns-Sayre syndrome

MD = Mitochondrial disorders

mtDNA = Mitochondrial DNA

nDNA = Nuclear DNA

NIHL = Noise-induced hearing loss

O_2 = Molecular oxygen

$O_2^{\cdot -}$ = Superoxide

PD = Parkinson's disease

PSP = Progressive supranuclear palsy

ROS = Reactive oxygen species

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