Send Orders for Reprints to reprints@benthamscience.ae

Current Neuropharmacology, **2019**, *17*, **21-32**

REVIEW ARTICLE

Anti-Oxidant Drugs: Novelties and Clinical Implications in Cerebellar Ataxias

Emanuele Barca[1,2,*], Valentina Emmanuele[1,2], Salvatore DiMauro[1], Antonio Toscano[2] and Catarina M. Quinzii[1]

[1]*Department of Neurology, Columbia University Medical Center, New York, NY, 10032, United States;* [2]*Department of Clinical and Experimental Medicine, University of Messina, Messina, 98125, Italy*

ARTICLE HISTORY

Received: June 17, 2017
Revised: October 28, 2017
Accepted: November 07, 2017

DOI:
10.2174/1570159X15666171109125643

Abstract: ***Background*:** Hereditary cerebellar ataxias are a group of disorders characterized by heterogeneous clinical manifestations, progressive clinical course, and diverse genetic causes. No disease modifying treatments are yet available for many of these disorders. Oxidative stress has been recurrently identified in different progressive cerebellar diseases, and it represents a widely investigated target for treatment.

***Objective*:** To review the main aspects and new perspectives of antioxidant therapy in cerebellar ataxias ranging from bench to bedside.

***Method*:** This article is a summary of the state-of-the-art on the use of antioxidant molecules in cerebellar ataxia treatments. It also briefly summarizes aspects of oxidative stress production and general characteristics of antioxidant compounds.

***Results*:** Antioxidants represent a vast category of compounds; old drugs have been extensively studied and modified in order to achieve better biological effects. Despite the vast body of literature present on the use of antioxidants in cerebellar ataxias, for the majority of these disorders conclusive results on the efficacy are still missing.

***Conclusion*:** Antioxidant therapy in cerebellar ataxias is a promising field of investigations. To achieve the success in identifying the correct treatment more work needs to be done. In particular, a combined effort is needed by basic scientists in developing more efficient molecules, and by clinical researchers together with patients communities, to run clinical trials in order to identify conclusive treatments strategies.

Keywords: Antioxidants, cerebellar ataxia, coenzyme Q_{10}, idebenone, ataxias, oxidative stress.

1. INTRODUCTION

Cerebellar ataxias (CAs) are a group of heterogeneous disorders clinically characterized by lack of motor coordination [1, 2]. CAs can be caused by acute structural cerebellar damage or by progressive cerebellar degeneration linked to an underlining genetic/metabolic disorder. Structural cerebellar damage caused by ischemia, hemorrhage, toxic diseases, immune-mediated damage has usually acute onset, and interventions aimed to remove or reduce the causative hit are able to stabilize the clinical course of ataxia [3].

CAs, due to genetic alterations, also referred as primary CAs (PCAs), are usually progressive neurodegenerative disorders with increased disability along the disease course. Because PCAs usually affect young adults and impair motor and cognitive function, the impact on quality of life is substantial.

Primary CAs are very heterogeneous in clinical presentation, disease progression, and pathophysiology. Because of the variegate mechanisms behind cerebellar degeneration, up to date no definite disease modifying therapies are available [4]. The main therapeutic strategies are based on rehabilitation and symptomatic approaches. Considering that cerebellar degeneration recognizes many primary causes, one reasonable approach would be to identify a recurrent pathway of cellular degeneration and develop drugs able to interfere with it. This strategy partially justifies the interest of antioxidant (AO) therapy in cerebellar ataxias. Oxidative stress, indeed, has been demonstrated in neurodegenerative disorders [5, 6] and in many forms of PCAs. The link between CAs and oxidative stress is also corroborated by the observa-

*Address correspondence to this author at the Department of Neurology, Columbia University Medical Center, 630 W 168th Street, P&S 4-424/A, New York, NY 10032, USA; Tel: +1-212-305-1637; Fax: +1-212-305-3986; E-mail: eb2877@cumc.columbia.edu

1570-159X/19 $58.00+.00

tion that genetic deficiency of natural cell antioxidants leads to phenotypes dominated by cerebellar ataxia (*e.g.* Vitamin E deficiency). The reason why cerebellum is more sensitive to oxidative stress and/or why there is more oxidative stress in cerebellum is still not completely understood but it is well known that Purkinje cells, the functional relay neurons of the cerebellar cortex, are one of the most energy-demanding cells of the organism [7].

Here, we will briefly review the main players in the oxidative stress cascade/response and the characteristics of the major antioxidant used in cerebellar ataxias (Fig. **1**). We will subsequently describe the different forms of cerebellar ataxias where AO have been used as a therapeutic approach.

2. FREE RADICALS AND OXIDATIVE STRESS

The production of free radicals is a known toxic property of partially reduced oxygen molecules. Free radicals derive from oxygen, hence Reactive Oxygen Species (ROS), and from nitrogen, Reactive Nitrogen Species (RNS). ROS are produced mostly in the mitochondria, and arise from the addition of electrons directly from the electron transport chain to O_2 leading to the formation of Superoxide ($O_2^{\bullet}$) [8, 9]. In mitochondria, substrates (*e.g.* glucose, fatty acid) are oxidized to produce ATP from ADP and inorganic phosphate [7, 10]. The final pathway of ATP production is located in the inner mitochondrial membrane (IMM) and is operated by four enzymatic complexes (complex I, II, III, IV) that shuttle electrons from substrates to oxygen molecule (O_2) to form H_2O. This electron flux is responsible for the generation of a proton gradient in the inner mitochondrial space that will be eventually used by complex V (ATP synthase) to synthetize ATP. However, this mechanism is not 100% efficient, and 1-5% of electrons interact directly with oxygen, producing reactive oxygen species (ROS) as a by-product of ATP production [11, 12].

The interaction between $O_2^{\bullet}$ and other molecules generates secondary reactive species causing a cascade of oxidation events. Another important player in the ROS cascade is hydroxyl radical ($^{\bullet}OH$) [9, 13]. To better understand the production of $^{\bullet}OH$ we have to introduce the role of iron. Iron "handling", in fact, is strictly controlled inside the cell and intracellular iron is always linked to proteins [14]. Excess in $O_2^{\bullet}$, however, is able to induce a release of iron from its carrier proteins; free iron participates then in the Fenton reaction generating $^{\bullet}OH$ from H_2O_2 [15]. As we move into the description of the disorders we will better underline this mechanism in Friederich ataxia (FA). The peroxyl radical ($ROO^{\bullet}$), another deleterious ROS, is the *primum movens* in oxidation of fatty acids [16]. Another, often overlooked, free radical family is composed by the Reactive Nitrogen Species

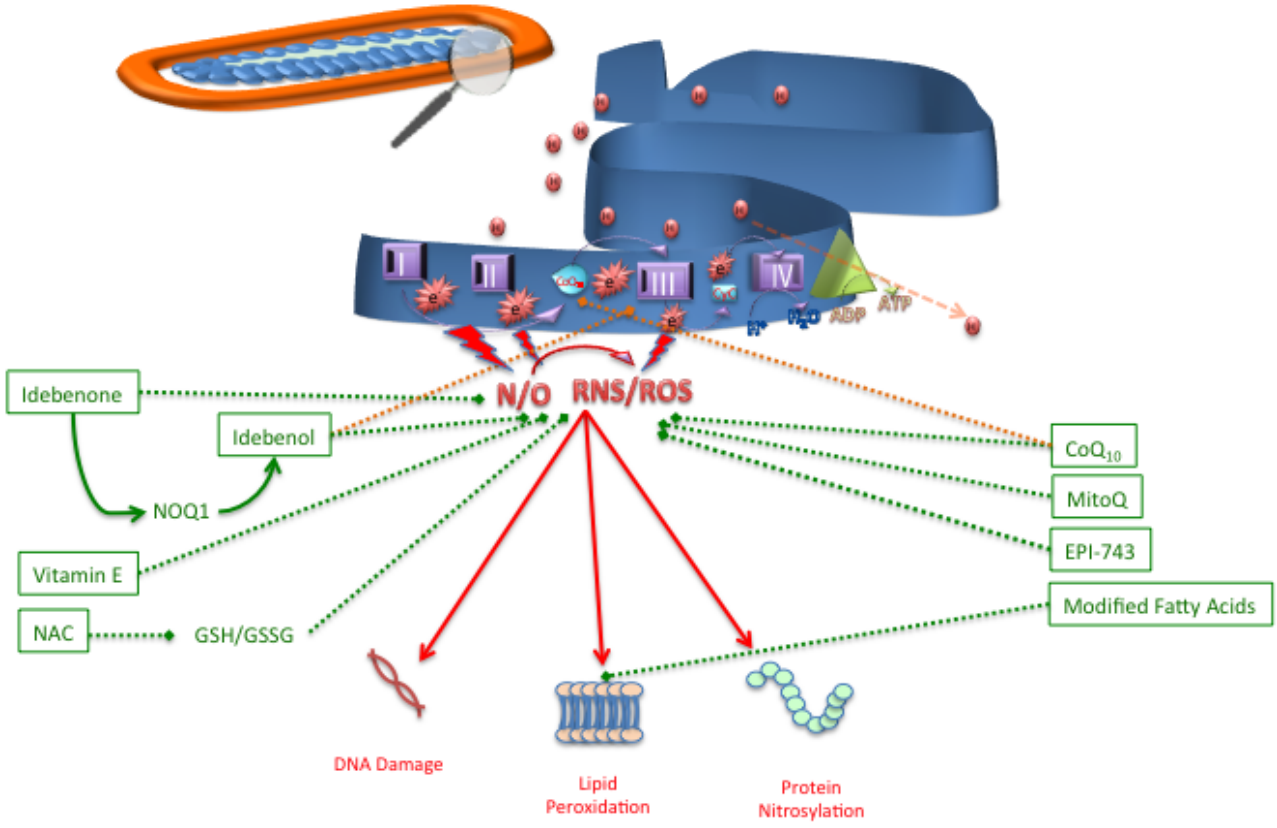

Fig. (1). Schematic representation of oxidative stress production and role of main antioxidant compounds used in cerebellar ataxia treatment. H^+, Protons; e-, Electron; I, Complex I; II, Complex II; III, Complex III; IV, Complex IV; CoQ_{10}, Coenzyme Q10; CyC, Cytochrome C; NOQ1, NAD(P)H:quinone acceptor oxidoreductase 1; NAC, N-Acetylcysteine; GSH/GSSG, Reduced/oxidized Glutathione; N/O, Nitrogen/Oxigen; RNS/ROS, Reactive Nitrogen Species/Reative Oxigen Species. (*The color version of the figure is available in the electronic copy of the article*).

(RNS) [17]. Nitric oxide ($NO^{\bullet}$) is the main RNS. It is produced by specific synthetases and act as a biological signal. Overproduction of $NO^{\bullet}$ causes uncontrolled nitrosylation reactions and secondary proteins structure alterations [18]. In some conditions, the simultaneous production of ROS and RNS can generate a highly oxidative molecule, peroxynitrite anion, which is able to damage DNA and lipids. At high concentrations, ROS and RNS react with purines, pyrimidines and even with the deoxyribose backbone. The most extensive studied DNA damage is the formation of 8-OH-Guanosine, which represents the first step of mutagenesis and carcinogenesis pathway. Interaction with lipids can form toxic aldehydes (*e.g.* malondialdehyde and 4-hydroxy-2-nonenal) that also present mutagenic capacities. Some aminoacids, especially cysteine and methionine, are susceptible to structural changes when exposed to ROS/RNS.

For many years the ROS/RNS production has been considered just as an inconvenient side effect of energy metabolism. However, it has emerged that small concentrations of ROS/RNS have a role in signaling, molecular biosynthesis, and detoxification reactions [19]. In summary, how do we define oxidative stress in the light of this dual behavior? Before the discovery of a physiological role of ROS, oxidative stress was simply defined as an imbalance between oxidative species and anti-oxidant mechanisms. This definition can be applied to diseases where natural cell antioxidants (Coenzyme Q_{10}, Vitamin E) are deficient and where the addition of the defective molecule to the system is able to rescue the damage. Nevertheless, in many other conditions the ROS/RNS damage cannot be simply restored by the use of antioxidants and this can be partially explained by the more complex role of ROS as signal molecules of the energy state of the cell. Nonetheless, the description of these mechanisms goes beyond the scope of our review, and will not be discussed further.

3. MAIN FAMILIES OF ANTIOXIDANTS COMPOUNDS

3.1. Coenzyme Q_{10} and its Analogs

Coenzyme Q (CoQ) is a polyprenyl quinone present in all cell membranes; it is also called ubiquinone or ubidecarenone, because of its widespread presence in living organisms [20]. The structure of CoQ consists of a "head", the benzoquinone ring, and a “tail” made of several isoprenyl residues. The most abundant ubiquinone in humans has 10 isoprenyl residues, and therefore is called CoQ_{10} [21]. CoQ_{10} is a highly lipophilic compound present in mitochondria where it functions as an electrons transporter within the IMM [22, 23]. Moreover, CoQ_{10} is able to cycle from an oxidized to a reduced form, thus playing an important role both as a direct antioxidant, buffering free electrons, and in restoring other cellular antioxidants, in particular, vitamin C and vitamin E. CoQ_{10} is synthetized de novo in the IMM by a multi-enzymatic complex. Defects in CoQ_{10} synthesis are rare and usually lead to severe multisystem disorders. Cerebellar ataxia is the most common symptoms in primary CoQ_{10} deficiency (*e.g. ADCK3* mutations) [24]. Moreover, the link between cerebellar degeneration and CoQ_{10} has been strengthened by the evidence of a secondary reduction of this compound in tissues from patients with other forms of ataxias (*e.g.* Apraxia with Oculomotor apraxia type 1, Anoctamin 10 mutations, Multi Systemic Atrophy) [25-28]. In line with these evidences, it is not surprising that CoQ_{10} has been largely used as treatment in many disorders with the aim of reducing oxidative stress and restoring energy production. CoQ_{10} has been proven safe in humans even at high doses (up to 3600 mg/day) [29], but the recommended dose is 2400 mg daily in adult and up to 30 mg/kg daily in pediatric patients [30]. CoQ_{10} should be taken with fat rich food and in multiple doses during the day to optimize the absorption. Unfortunately, CoQ_{10} has many chemical and physical characteristics that importantly reduce its bioavailability. In pharmaceutical preparation, CoQ_{10} is sensitive to air, ultraviolet light and high temperature [31]; moreover, it is poorly absorbed because of its low solubility in water [20]. CoQ_{10} is also difficult to deliver to the mitochondria, the primary site of its biological actions, because of the high molecular weight and the high affinity for membrane lipids, leading to a low perfusion within the biological membrane (*e.g.* blood brain barrier) and within sub-cellular compartments [32]. For this reason many efforts have been made to develop compounds that share the same biologic features of CoQ_{10} but with improved bioavailability.

Idebenone has been synthetized for the first time in Japan in 1984 [33]. It is one of many CoQ_{10} analogues with a modified tail in order to achieve a better bioavailability, especially in nervous tissues [34]. It has a predicted antioxidant activity being able to detoxify many free radicals included the dreaded peroxynitrites [35]. Idebenone crosses the blood-brain barrier following oral administration and is well tolerated in humans even at high dosages (1000-2000 mg), with a linear pharmacokinetics [36]. Although it appears as the perfect antioxidant drug, the results of clinical trials in humans did not show striking efficacy data. The disease where idebenone has been extensively studied is Friederich ataxia and we will cover this in details later. Many patients with other oxidative stress related neurodegenerative disorders (*e.g.* Alzheimer disease, Huntington disease, *etc.*) have been given idebenone without obtaining clear long term effects on the disease course [37]. Idebenone has been also studied in mitochondrial diseases as Mitochondrial Lactic Acidosis and Stroke-like Episodes (MELAS) and it is now under investigation in Duchenne muscular dystrophy [37]. Efficacy of idebenone as disease modifying therapy has been demonstrated in a subgroup of patients with Leber Hereditary Optic Neuropathy (LHON) [38-40]. Considering its biochemical structure, it is reasonable to think that idebenone is able to substitute CoQ_{10} in shuttling electrons from Complex I and II to complex III of the respiratory chain, but many experimental data excluded this hypothesis [41]. It has also been demonstrated *in vitro* that idebenone can act as pro-oxidant by binding a non-physiological site of Complex I, competing with CoQ_{10} and generating $O_2^{\bullet}$ [42]. This apparently contradicting function can explain the non-clear efficacy of idebenone in clinical trials. Recent studies have demonstrated that idebenone is reduced to idebenol that exerts antioxidant activity. This process is catalyzed by an inducible enzyme present in cytoplasm, NQO1 (NAD(P)H: quinone acceptor oxidoreductase 1). Interestingly, NQO1 is highly expressed in glial cells but not in normal neurons, and

its expression increases in conditions of increased oxidative stress. The identification of NQO1 opens the way to the investigation of combination therapies of idebenone and drugs that increase NQO1 through the up regulation of the oxidative stress pathway [43]. These compounds (*e.g*. carnosic acid, NEPPs) may be used in the future as efficient combined antioxidant approaches.

The most recent CoQ_{10} analogs are A0001 (α-tocopherylquinone) and EPI-743. A0001 is a molecule that shares structural similarities with CoQ_{10}, but differs for the chemical substituents of the benzoquinone ring. As a consequence, A0001 should present a more favorable redox potential than CoQ_{10}. A0001 is expected to mitigate oxidative stress and lipid peroxidation, and to facilitate electron transfer in respiratory chain defects. A0001 is present in very low levels in the blood of mammals [44]. Although A0001 can be produced by metabolism of vitamin E, studies using labeled metabolites demonstrated that A0001 is synthetized de novo from tyrosine and mevalonic acid [45]. A0001 was well tolerated at high dosage (up to 6 gr), except for a prolongation of coagulation time, and exhibited a good pharmacokinetic profile [46]. A0001 has been used in FA (see specific FA section) [47]. EPI-743 has recently replaced A0001 in clinical trials [48]. EPI-743 has been developed from a series of para-benzoquinone analogs that differ in the quinone ring and the structure of the lipid chain [49]. EPI-743 has a more powerful redox potential than CoQ_{10} thus better scavenging oxidative stress. EPI-743 has been used in different small mitochondrial diseases trials with preliminary positive results [50, 51]; interesting data suggest an *in vivo* effect of EPI-743 in reducing oxidative stress biomarkers (SPECT with HMPAO) in cerebellum of patients with mitochondrial diseases [50].

3.2. MitoQ

Since one of the drawbacks of antioxidant drugs is delivering these exogenous compounds into the areas where ROS/RNS are produced the most, the inner mitochondrial membrane several studies have been focused on modifying molecules in order to make them concentrate following the proton gradient on IMM [52, 53]. By adding a triphenylphosphonium lipophilic cation (TPP), it is possible to increase the membrane passage of therapeutic molecules and to accumulate them in the mitochondrial matrix in response to the membrane potential [54]. MitoQ is a ubiquinone linked to a TPP [55]. MitoQ, as well as CoQ_{10}, is able to cycle from a reduced, ubiquinol, to an oxidized, ubiquinone state thus functioning as ROS/RNS scavengers [56]. In addition, MitoQ is able to easily penetrates into the IMM [57]. Several studies conducted on animal models of human diseases have proven MitoQ safe and effective in reducing oxidative stress [54]. Clinical trials conducted in patients affected by Parkinson Disease (PD) demonstrated that MitoQ could be safely administered in humans [58].

3.3. Vitamin E

The term vitamin E (VitE) refers to many different fat-soluble compounds belonging to the family of tocopherols and tocotrienols [59]. They are synthetized in plants, and they are present in many seed oils, green vegetables, nuts, dairy products, meat and fish [60]. VitE is an essential nutrient that functions as anti-oxidant principally against the formation of lipid peroxyl radicals [61]. Adequate levels of VitE are essential for normal human cells functioning but it is in central nervous system that VitE plays its major role [62]. VitE is taken up by tissues *via* a specific transporter (tocopherol transfer protein, TTP). Molecular defects in this transporter lead to ataxia with vitamin E deficiency (AVED) [63]. VitE is able to cross the blood-brain barrier [64], but a consensus on its bioavailability after oral intake is still missing (values range from 10% to 79%) [65].

VitE is crucial for neuron physiology and some experimental data demonstrate the ability of neural cells to store vitamin E in membrane compartments [66, 67]. As for idebenone, the complete range of VitE functions is not completely uncovered. There is vast evidence that demonstrates the role of vitamin E in preventing oxidative stress, mainly in mitochondria of high oxygen consuming tissues as brain [6] and retina [68]. In recent years, novel functions of α-tocopherol have been discovered, and VitE seems to be involved in signaling cascades and gene regulation. Many of these functions occur in the nervous system [62]. Considering the importance of VitE for nervous system and its antioxidant action, supplementation with this compound has been attempted in many disorders including Alzheimer disease (AD), Parkinson diseases (PD), Down syndrome [62], and Amyotrophic Lateral Sclerosis (ALS) [69]. In neurologic disorders where VitE is specifically reduced (AVED and abetalipoproteinemia), the supplementation is able to strikingly ameliorate the phenotype [70]. As far as safety is concerned, VitE is one of the least toxic vitamins. Care should be applied when using high doses of VitE in patients with coagulation disorders, since it could alter absorption of other fat-soluble vitamins (vitamin A, D and K). High intakes of VitE, if not correctly balanced by other antioxidant systems (*e.g*. vitamin C) could also have a pro-oxidant effect [71].

3.4. N-AcetylCysteine

N-AcetylCysteine (NAC) is a well-known drug used as a safe mucolytic [72] and as an antidote in acetaminophen overdose [73]. In the context of this review, NAC will be discussed for the strong anti-oxidant action that makes it an appealing drug for the treatment of some cerebellar disorders. NAC is a cysteine precursor that differs from cysteine, as it is membrane permeable and does not require any transporter [74]. The anti-oxidant effect of NAC is achieved by providing cysteine to glutathione (GSH).

GSH is synthesized in the cell by two enzymes, glutamylcysteine synthetase and GSH synthetase. Cysteine is usually the limiting precursor that regulates GSH synthesis [75]. GSH works as a free radicals scavenger, representing a major component of the oxidative stress regulating system [76]. Unfortunately, NAC has low bioavailability in tissues due, primarily, to its low lipophilicity. The blood brain barrier (BBB) permeability of NAC is disputed, and it appears that different administration routes can give different results in allowinging NAC into the nervous system; for example, in an experimental animal model, the intravenous injection of NAC achieved a good BBB permeability, while the intraperitoneal injection did not [74]. NAC is generally safe and

well tolerated even at high doses; frequent side effects are gastrointestinal (nausea, vomiting, and diarrhea), or allergic reactions after intravenous injection. Particular precautions should be used in patients with heart diseases since NAC can increase the efficacy of nitrates. The use of NAC has been investigated in patients with AD, PD, Huntignton diseases, Down syndrome, and ALS with promising but not definite results [74]. Despite the interesting properties and the encouraging experimental results, clinical data on the use of NAC in cerebellar ataxias are based mainly on anecdotal reports. NAC has been used in patients with Friederich ataxia, Ataxia-Teleangectasia, and Multiple System Atrophy and has shown some clinical benefits. Details of NAC use in ataxic disorders will be discussed in the disease specific subchapters. New modified forms of NAC are currently under investigation: N-acetylcysteine ethyl ester (NACET) [77] and N-acetylcysteine amide (NACA) [78]. They should overcome the low bioavailability of NAC increasing the amount of cysteine reaching brain tissues thus showing a higher anti-oxidant effect in the target tissues [79].

3.5. Modified Fatty Acids

This group of compounds represents a quite new strategy and a promising weapon against lipid oxidative stress. We already described the role of ROS/RNS in oxidizing membranes lipids. Lipid-peroxidation represents a crucial step in ROS/RNS cell damage. Oxidized lipids can initiate a cascade of reactions that leads to irreversible cell damage and apoptosis [80]. Notably, brain tissue is rich in fatty acid and therefore more prone to lipid-peroxidation [81]. Moreover, mitochondrial membrane contains cardiolipin, a phospholipid that, when oxidized, triggers apoptosis [82]. Fatty acids present in the CNS are composed prevalently by polyunsaturated fatty acids (PUFAs); also cardiolipin contains PUFAs in its molecular structure. It is consequential that protecting PUFAs from oxidative stress may represent a therapeutic target in neurodegenerative disorders. Interestingly, a specific isotopic modification (deuteration) of PUFAs such as linoleic acid (C18:2, n-6) and α-linolenic acid (C18:3, n-3) is able to protect PUFAs from oxidation preventing the cascade of deleterious events [83]. Deuteration of PUFAs has been applied in models of FA with promising results [84].

4. ANTIOXIDANT THERAPEUTIC APPROACHES IN CEREBELLAR ATAXIAS

In this section, we will provide an overview of the specific use of antioxidants in different cerebellar ataxias. Antioxidants have been used in CAs with primary deficit of antioxidant (ataxia with CoQ_{10} deficiency, AVED) and CAs with documented oxidative stress. In the first group, antioxidants represent the main approach and usually induce a more dramatic clinical response; in the second group of diseases, clinical results are less striking.

4.1. Ataxia with Primary CoQ_{10} Deficiency (ARCA2)

Disorders of CoQ_{10} synthesis and its regulation lead to a large spectrum of diseases, called primary CoQ_{10} deficiencies, to differentiate them from disorders where CoQ_{10} is reduced but its biosynthetic pathway is not altered [24], as Ataxia with oculomotor apraxia 1 (AOA1), or Anoctamine

Table 1. Summary of antioxidants clinical trials on cerebellar ataxias.

Disease	Drug	Dosage	Outcome/Status	Refs.
ARCA2	Idebenone	up to 700 mg/day	Beneficial in 1/8; unsuccessful in 7/8 (deleterious in 2/7)	[86-90]
-	CoQ_{10}	up to 1200 mg/day	Beneficial in 7/17; unsuccessful in 9/17 (deleterious in 2/17)	[86-90]
-	Deoxy-ubiquinone	1000 mg/day	1/1 unsuccessful	[87]
AVED	VitE	800-1500 mg/day	Effective (SOC)	[97]
FA	Idebenone	180-2250mg/day	No changes in primary outcomes; unclear results in secondary outcomes	[104]
-	CoQ_{10} and VitE	CoQ10 600 mg/day plus VitE 2100 IU/day	No changes in primary outcomes; unclear results in secondary outcomes	[104]
-	A0001	1 g/day or 1.5 g/day	Positive effects on neurological outcome measures	NCT01035671
-	EPI743	200mg/day or 400 mg/day	Phase 2 clinical trial completed, but data not available	NCT01728064
SCA (SCA1, 2, 3,6)	CoQ_{10}	100-2400 mg/day	SCA1 and 3: better clinical outcome at baseline, but no changes in disease progression; SCA2 and 6: unsuccessful	[108]
-	Vitamin E	unknown	Unsuccessful	[108]
AOA1	CoQ_{10}	200-3000 mg/day	Beneficial in increasing energy level and reducing frequency of seizures in anecdotal cases	[123]
-	CoQ_{10}	150 mg/day or 300 mg/day	Phase 3 clinical trial currently recruiting	NCT0233305

Abbreviations: ARCA2: Autosomal Recessive Cerebellar Ataxia type 2; CoQ_{10}: Coenzyme Q_{10}; AVED: Ataxia with Vitamin E Deficiency; VitE: Vitamin E; SOC: Standard of Care; FA: Friedreich's Ataxia; SCA: SpinoCerebellar Ataxia; AOA1: Ataxia with Oculomotor Apraxia type 1.

10 (SCAR10). The majority of patients with primary CoQ_{10} deficiency have cerebellar ataxia and the most common molecular defects are mutations in *ADCK3* (*COQ8A*). The role of ADCK3 is still not completely understood. It is known that ADCK3 participates in CoQ_{10} biosynthesis regulating and stabilizing the multimeric complex responsible for CoQ_{10} synthesis. Mutations in *ADCK3* cause autosomal recessive cerebellar ataxia type 2 (ARCA2) [85]. ARCA2 is a rare disorder and up to date only 46 patients have been reported in the literature. Phenotypically, patients with ARCA2 have a large variability in diseases onset, ranging from infancy to late adulthood, and severity, ranging from pure ataxic forms to severe forms with central nervous system involvement with seizures and stroke-like lesions [86]. Considering the few individuals affected, currently no systematic clinical trials have been conducted. Since ARCA2 biochemical hallmark is the reduction of CoQ_{10} in different tissues (mainly skeletal muscle), the logical therapeutic approach is CoQ_{10} oral supplementation. Data retrieved from the literature review indicate that results on treatments are available in 26 patients [86-90]. Eight out of the 26 patients received idebenone (dose up to 700 mg per day): one patient showed an improvement of ataxic syndrome while the treatment was unsuccessful in the remaining 7 patients and even harmful in 2 subjects [86]. Supplementation of CoQ_{10} in 17 patients (dose up to 1200 mg/day) showed improvement of neurological condition in 7 of them; only two patients had to withdraw treatment because of side effects (anorexia and diarrhea) [86]. One patient was treated with deoxyubiquinone with no beneficial effect [87]. Therefore, it appears that CoQ_{10} should be preferred over idebenone in treating such disorder. The variability in the response to CoQ_{10} supplementation can be explained by many factors: 1) the low bioavailability of this molecule in the nervous tissue, as previously discussed [91], 2) the possible involvement of ADCK3 in functions other than CoQ_{10} biosynthesis regulation in the cerebellum [92]; 3) the possible role of CoQ_{10} deficiency in cell damage due to extra-respiratory chain function of CoQ_{10} [93, 94]; 4) the slowly progressive course of ARCA2 that requires longer follow-up to detect treatment effects [86]. The reduced form of CoQ_{10}, ubiquinol, has shown better efficiency in treating a mouse model of CoQ_{10} encephalopathy, and it may represent a promising future approach for this disorder [95] (Table **1**).

4.2. Ataxia with Vitamin E Deficiency

Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive disorder due to mutation in the α-tocopherol transfer protein (TTP). TTP is mainly expressed in the liver and facilitates vitamin E transport into the plasma. Loss of TTP function causes severe reduction of plasma vitamin E leading to a Friederich-like hereditary cerebellar ataxia with deep sensory loss, pyramidal tract involvement, and retinitis [96]. Patients with AVED rarely present with intellectual decline, and may manifest arm or cervical dystonia [70]. Treatment of choice is supplementation with high dose vitamin E. Restoring vitamin E plasma levels produces a dramatic clinical response; treatment started in early stages is able to reverse ataxia. It has also been recently reported that vitamin E supplementation in pre-symptomatic individuals is able to prevent disease manifestations [97]. Treatment with vitamin E is safe. Recommended doses range from 800 mg to 1500 mg per day or 40 mg/kg of body weight in children, and plasma levels of Vitamin E should be checked every 6 months. Particular care should be taken in handling plasma samples to avoid that oxidation of vitamin E can alter test results.

4.3. Friederich Ataxia

Friederich Ataxia (FA) is a rare autosomal recessive disorder characterized by ataxia associated with cardiac dysfunction. Although a rare disease, FA is the most common cause of autosomal recessive cerebellar ataxia with a prevalence of 1/50,000 in the European population [98]. The disease is progressive, leading to the loss of ambulation at young age (late teens) and death most commonly occurs for heart failure. The disease is caused by the reduction of the protein frataxin that is located in the mitochondria and regulates the influx of iron as well as sulfide production [99]. Reduction in frataxin levels leads to loss of Fe-S clusters of the mitochondrial respiratory chain complexes leading to mitochondrial dysfunction, reduced ATP production and increased oxidative damage [100]. Considering the pathophysiology of this disease, different antioxidant treatments have been tested in patients with FA. The main antioxidants used in FA are idebenone and CoQ_{10}. Studies on these drugs have been conducted since the early 1990s. Three main trials have been published with at least 12 months follow up; two of these trials compared idebenone to placebo [101, 102] and one compared high dose CoQ_{10} to a regimen of low dose CoQ_{10} and vitamin E considered as placebo [103]. Main outcome measures were neurological and cardiac functions. Progression of ataxia was monitored by specific scores (International Cooperative Ataxia Rating Scale, ICARS), and no changes were detected after treatment. Ejection fraction, fractional shortening, and intraventricular-septal thickness were evaluated as markers of cardiac function but the results were discordant among studies and lacked of statistical significance. Promising data were obtained on the reduction of overall cardiac mass in patients treated with idebenone, but considering the complexity of myocardial involvement in FA, more studies are needed to confirm these findings [104]. Idebenone has been used in phase III trials in other short-term follow-up studies with no improvement on the neurologic status and heart function [105]. Other antioxidants have been used in FA patients although in smaller cohorts. For instance, A0001 has been administered for 4 weeks in 31 patients with FA showing positive effects on the neurological outcome measures [47].

4.4. Spinocerebellar Ataxias

Spinocerebellar ataxias (SCAs) are a group of heterogeneous autosomal dominant progressive cerebellar ataxias, manifesting as gate unsteadiness, dysarthria, and loss of hand agility. The historical term "SCA" was first used in the 50s and up to date 40 SCAs have been identified and numbered in order of discovery [106]. The cerebellar phenotype is often associated with complex multisystemic neurological deficits, such as cognitive impairment, ophthalmoparesis, and pyramidal and extrapyramidal signs. Atrophy of cerebellum and brainstem is a characteristic feature of SCAs, and

the involvement of other brain structures accounts for the clinical heterogeneity of these disorders. Onset of symptoms is usually during the third or fourth decade of life, although onset in childhood or late adulthood has also been described.

Association with more than 30 genes/loci has been so far described in these disorders and mutations can be classified in expansions of coding CAG repeats (polyglutamine expansion SCAs), expansions of non-coding regions (non-coding-expansion SCAs), and point mutations. Phenotypic variability exists not only among patients with different disease-causing genes, but also among patients with mutations in the same gene [107]. The phenotypic and genetic heterogeneity of these disorders represents a challenge to the development of a therapy, and no specific treatment can currently prevent, delay, or reverse the phenotype of SCAs. AOs have been recently proposed as a therapeutic option in SCAs. R.Y. Lo and colleagues studied the longitudinal effects of CoQ_{10} and Vitamin E, among over candidate drugs, in a cohort of patients with the most common types of SCAs (SCA1, 2, 3, and 6) [108]. The severity of the ataxia was assessed for 2 years using the Scale for Assessment and Rating of Ataxia (SARA) scores as primary outcome. The authors found that CoQ_{10} exposure was associated with better clinical status in SCA1 and SCA3 at baseline, but did not modify the disease progression during the 2 years of follow-up, concluding that a clinical trial is needed to better determine the effect of CoQ_{10} in patients with SCAs. Interestingly, mitochondrial alterations have been lately described in a SCA1 mouse model [109]. The administration of oral MitoQ was able to restore mitochondrial function in older symptomatic mice, and slowed down the development of disease progression in younger mice before mitochondrial deficits appeared. Remarkably, Purkinje cells degeneration, a hallmark of the disease also in humans, was reduced.

4.5. Ataxia Teleangectasia

Ataxia Teleangectasia (AT) is an autosomal recessive disorder due to mutations in ATM gene [110]. From a clinical point of view, this disorder is characterized by neurodegeneration with progressive cerebellar ataxia, oculo-cutaneous telangiectasia, immunodeficiency, premature aging, and an increased predisposition to malignancies. ATM belongs to a family of large proteins involved in cell-cycle control and cellular responses to DNA damage maintenance. AT cells are particularly prone to apoptosis, especially naive T cells and Purkinje cells. Although the exact mechanism behind apoptotic cell death in AT is still poorly understood, it has been demonstrated both *in vitro* and in animal models that ATM deficient cells are particularly sensitive to ROS damage [111]. The mechanisms behind the increased ROS sensitivity in ATM deficient organisms are various, and range from lack of an efficient ROS protection response [112] to mitochondrial respiratory chain dysfunction [113]. Oxidative stress has been also described in patients with AT, as demonstrated by the presence of different markers of oxidative damage as well as the reduction of some non-enzymatic antioxidant in blood [114, 115]. Different antioxidant treatments (*e.g*. NAC) have been evaluated in AT murine model with promising results, such as a reduced rate of tumorigenesis and increased lifespan [116]. Despite the promising preclinical data, to date no systematic clinical trial has been conducted to analyze the effect of antioxidants in AT patients [111].

4.6. Ataxia with Oculomotor Apraxia Type 1

Ataxia with oculomotor apraxia type (AOA1) is an autosomal recessive disorder characterized by early onset cerebellar ataxia, oculomotor apraxia, and peripheral neuropathy due to mutation in the *APTX* gene, which encodes aprataxin, a protein involved in DNA single-strand break repair [117-119]. Impaired oxidative stress response has been widely demonstrated in a large portion of AOA1 patients [120]. In particular, a moderate reduction of CoQ_{10} levels has been identified both in muscle and in primary fibroblasts derived from AOA1 patients [26, 121]. Recent data suggest that aprataxin plays a direct role in regulation of mitochondrial function [122] and in regulation of CoQ_{10} biosynthetic genes transcription [123]. CoQ_{10} supplementation has been used in few AOA1 patients and seems to be associated with some degree of clinical efficacy especially on subjective outcomes, such as overall energy levels, and on the frequency of the epileptic seizures [123]. A phase III clinical trial on CoQ_{10} in AOA1 patients is currently recruiting and is expected to be completed by September 2017 (ClinicalTrials.gov NCT02333305).

4.7. Multiple System Atrophy

Multiple System Atrophy (MSA) is a rare and fatal neurodegenerative disorder, characterized by parkinsonism, cerebellar impairment, and autonomic dysfunction [124]. MSA, together with PD and dementia with Lewy bodies, has as a neuropathological hallmark the build-up of synuclein in the brain. It is still debated if the cytoplasmatic glial accumulation of alpha-synuclein is the primary cause of the diseases or rather a result of neural degeneration [125]. Oxidative stress and mitochondrial dysfunction seem to play a role in MSA pathogenesis [126]. The genetic cause of MSA is not known yet, but mutations in *COQ2*, encoding the second enzyme of CoQ_{10} biosynthesis, have been reported in patients with familiar MSA [127]. Although at the moment the data on the association between *COQ2* genetic variants and MSA are conflicting [128, 129], post-mortem studies showed reduced CoQ_{10} levels in brains of MSA patients without mutations in *COQ2* [27, 28], confirming the role of CoQ_{10} deficiency in MSA [27]. Moreover, reduced levels of plasma CoQ_{10} have been found in patients with MSA [130]. Since no disease modifying therapies are currently available for MSA patients, drugs targeting oxidative stress, and in particular CoQ_{10} synthesis, could be an interesting field of investigation.

CONCLUSION

Cerebellar ataxias are a very heterogeneous group of neurodegenerative disorders from a clinical and genetic point of view. The mechanisms leading to cerebellar degeneration are still not completely unraveled, but oxidative stress seems to be an important actor playing a primary role in cellular damage in some CAs, and contributing to the pathology development in others. Therefore, free radical production and oxidative stress have been a privileged therapeutic target in CAs, although results in clinical setting are mainly anecdotal and the few clinical trials were inconclusive [50]. As widely

discussed in this review, different complications burden the development of an antioxidant therapy and the correct evaluation of its efficacy. Among the hardest challenges is the ability to deliver antioxidant compounds to the site of free radical production; the "ideal" drug should cross the blood-brain barrier and different cellular membranes to reach the mitochondrial matrix. Moreover, since neurons are stable cells, timing of therapy initiation is crucial. Unfortunately, for the majority of CAs, treatment is started when the symptoms are already present and cellular damage is at an advanced stage, thus limiting the benefits.

Many compounds with promising preclinical properties are currently in the development pipeline, and great effort must be dedicated in designing good phase III clinical trials with sensitive outcome measures apt to detect clinical changes in these rare, slowly progressive, long-course disorders.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Emanuele Barca and Valentina Emmanuele are supported by the North American Mitochondrial Diseases Consortium (NAMDC) fellowship program 2017-2018 and 2016-2017 respectively. V.E. has also been supported by L`Oréal-UNESCO for Women in Science 2016, Italy. A.T., C.M.Q. and S.D. have no conflict of interest.

ACKNOWLEDGMENTS

Emanuele Barca contributed on the conception and design of the work, data analysis, literature review and drafting the article. Valentina Emmanuele contributed in literature research, data analysis ad drafting the manuscript. Antonio Toscano, Catarina M. Quinzii and Salvatore DiMauro contributed in critical revision of the manuscript and data analysis. All the authors approved the final version of the manuscript.

REFERENCES

[1] Bodranghien, F.; Bastian, A.; Casali, C.; Hallett, M.; Louis, E.D.; Manto, M.; Mariën, P.; Nowak, D.A.; Schmahmann, J.D.; Serrao, M.; Steiner, K.M.; Strupp, M.; Tilikete, C.; Timmann, D.; van Dun, K. Consensus paper: Revisiting the symptoms and signs of cerebellar syndrome. *Cerebellum,* **2016**, *15*(3), 369-391. [http://dx.doi.org/10.1007/s12311-015-0687-3] [PMID: 26105056]

[2] Manto, M.; Haines, D. Cerebellar research: two centuries of discoveries. *Cerebellum,* **2012**, *11*(2), 446-448. [http://dx.doi.org/10.1007/s12311-011-0336-4] [PMID: 22113501]

[3] Manto, M. The cerebellum, cerebellar disorders, and cerebellar research--two centuries of discoveries. *Cerebellum,* **2008**, *7*(4), 505-516. [http://dx.doi.org/10.1007/s12311-008-0063-7] [PMID: 18855093]

[4] Ilg, W.; Bastian, A.J.; Boesch, S.; Burciu, R.G.; Celnik, P.; Claaßen, J.; Feil, K.; Kalla, R.; Miyai, I.; Nachbauer, W.; Schöls, L.; Strupp, M.; Synofzik, M.; Teufel, J.; Timmann, D. Consensus paper: Management of degenerative cerebellar disorders. *Cerebellum,* **2014**, *13*(2), 248-268. [http://dx.doi.org/10.1007/s12311-013-0531-6] [PMID: 24222635]

[5] Giannoccaro, M.P.; La Morgia, C.; Rizzo, G.; Carelli, V. Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson's disease. *Mov. Disord.,* **2017**, *32*(3), 346-363. [http://dx.doi.org/10.1002/mds.26966] [PMID: 28251677]

[6] Islam, M.T. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurol. Res.,* **2017**, *39*(1), 73-82. [http://dx.doi.org/10.1080/01616412.2016.1251711] [PMID: 27809706]

[7] Zeviani, M.; Simonati, A.; Bindoff, L.A. Ataxia in mitochondrial disorders. *Handb. Clin. Neurol.,* **2012**, *103*, 359-372. [http://dx.doi.org/10.1016/B978-0-444-51892-7.00022-X] [PMID: 21827900]

[8] Miller, D.M.; Buettner, G.R.; Aust, S.D. Transition metals as catalysts of "autoxidation" reactions. *Free Radic. Biol. Med.,* **1990**, *8*(1), 95-108. [http://dx.doi.org/10.1016/0891-5849(90)90148-C] [PMID: 2182396]

[9] Pastor, N.; Weinstein, H.; Jamison, E.; Brenowitz, M. A detailed interpretation of OH radical footprints in a TBP-DNA complex reveals the role of dynamics in the mechanism of sequence-specific binding. *J. Mol. Biol.,* **2000**, *304*(1), 55-68. [http://dx.doi.org/10.1006/jmbi.2000.4173] [PMID: 11071810]

[10] DiMauro, S.; Schon, E.A.; Carelli, V.; Hirano, M. The clinical maze of mitochondrial neurology. *Nat. Rev. Neurol.,* **2013**, *9*(8), 429-444. [http://dx.doi.org/10.1038/nrneurol.2013.126] [PMID: 23835535]

[11] Indo, H.P.; Yen, H.C.; Nakanishi, I.; Matsumoto, K.; Tamura, M.; Nagano, Y.; Matsui, H.; Gusev, O.; Cornette, R.; Okuda, T.; Minamiyama, Y.; Ichikawa, H.; Suenaga, S.; Oki, M.; Sato, T.; Ozawa, T.; Clair, D.K.; Majima, H.J. A mitochondrial superoxide theory for oxidative stress diseases and aging. *J. Clin. Biochem. Nutr.,* **2015**, *56*(1), 1-7. [http://dx.doi.org/10.3164/jcbn.14-42] [PMID: 25834301]

[12] Indo, H.P. Hawkins, C. L.; Nakanishi, I.; Matsumoto, K. I.; Matsui, H.; Suenaga, S.; Davies, M. J.; St Clair, D. K.; Ozawa, T.; Majima, H. J. Role of mitochondrial reactive oxygen species in the activation of cellular signals, Molecules, and Function. *Handb. Exp. Pharmacol.,* **2017**, *240,* 439-456.

[13] Finkel, T.; Holbrook, N.J. Oxidants, oxidative stress and the biology of ageing. *Nature,* **2000**, *408*(6809), 239-247. [http://dx.doi.org/10.1038/35041687] [PMID: 11089981]

[14] Petrat, F.; de Groot, H.; Rauen, U. Subcellular distribution of chelatable iron: a laser scanning microscopic study in isolated hepatocytes and liver endothelial cells. *Biochem. J.,* **2001**, *356*(Pt 1), 61-69. [http://dx.doi.org/10.1042/bj3560061] [PMID: 11336636]

[15] Kakhlon, O.; Cabantchik, Z.I. The labile iron pool: characterization, measurement, and participation in cellular processes(1). *Free Radic. Biol. Med.,* **2002**, *33*(8), 1037-1046. [http://dx.doi.org/10.1016/S0891-5849(02)01006-7] [PMID: 12374615]

[16] De Grey, A.D. HO_2*: the forgotten radical. *DNA Cell Biol.,* **2002**, *21*(4), 251-257. [http://dx.doi.org/10.1089/104454902753759672] [PMID: 12042065]

[17] Bhatti, J.S.; Bhatti, G.K.; Reddy, P.H. Mitochondrial dysfunction and oxidative stress in metabolic disorders - A step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta Mol. Basis Dis,* **2017**, *1863*(5), 1066-1077. [http://dx.doi.org/10.1016/j.bbadis.2016.11.010] [PMID: 27836629]

[18] Ridnour, L.A.; Thomas, D.D.; Mancardi, D.; Espey, M.G.; Miranda, K.M.; Paolocci, N.; Feelisch, M.; Fukuto, J.; Wink, D.A. The chemistry of nitrosative stress induced by nitric oxide and reactive nitrogen oxide species. Putting perspective on stressful biological situations. *Biol. Chem.,* **2004**, *385*(1), 1-10. [http://dx.doi.org/10.1515/BC.2004.001] [PMID: 14977040]

[19] Jones, D.P. Redefining oxidative stress. *Antioxid. Redox Signal.,* **2006**, *8*(9-10), 1865-1879. [http://dx.doi.org/10.1089/ars.2006.8.1865] [PMID: 16987039]

[20] Bhagavan, H.N.; Chopra, R.K. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic. Res.,* **2006**, *40*(5), 445-453. [http://dx.doi.org/10.1080/10715760600617843] [PMID: 16551570]

[21] Matthews, R.T.; Yang, L.; Browne, S.; Baik, M.; Beal, M.F. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc. Natl. Acad. Sci. USA,* **1998**, *95*(15), 8892-8897. [http://dx.doi.org/10.1073/pnas.95.15.8892] [PMID: 9671775]

[22] Beyer, R.E. An analysis of the role of coenzyme Q in free radical generation and as an antioxidant. *Biochem. Cell Biol.,* **1992**, *70*(6), 390-403. [http://dx.doi.org/10.1139/o92-061] [PMID: 1333230]

[23] Ernster, L.; Dallner, G. Biochemical, physiological and medical aspects of ubiquinone function. *Biochim. Biophys. Acta,* **1995**, *1271*(1), 195-204. [http://dx.doi.org/10.1016/0925-4439(95)00028-3] [PMID: 7599208]

[24] Quinzii, C.M.; Emmanuele, V.; Hirano, M. Clinical presentations of coenzyme q10 deficiency syndrome. *Mol. Syndromol.,* **2014**, *5*(3-4), 141-146. [http://dx.doi.org/10.1159/000360490] [PMID: 25126046]

[25] Balreira, A.; Boczonadi, V.; Barca, E.; Pyle, A.; Bansagi, B.; Appleton, M.; Graham, C.; Hargreaves, I.P.; Rasic, V.M.; Lochmüller, H.; Griffin, H.; Taylor, R.W.; Naini, A.; Chinnery, P.F.; Hirano, M.; Quinzii, C.M.; Horvath, R. ANO10 mutations cause ataxia and coenzyme Q10 deficiency. *J. Neurol.,* **2014**, *261*(11), 2192-2198. [http://dx.doi.org/10.1007/s00415-014-7476-7] [PMID: 25182700]

[26] Quinzii, C.M.; Kattah, A.G.; Naini, A.; Akman, H.O.; Mootha, V.K.; DiMauro, S.; Hirano, M. Coenzyme Q deficiency and cerebellar ataxia associated with an aprataxin mutation. *Neurology,* **2005**, *64*(3), 539-541. [http://dx.doi.org/10.1212/01.WNL.0000150588.75281.58] [PMID: 15699391]

[27] Barca, E.; Kleiner, G.; Tang, G.; Ziosi, M.; Tadesse, S.; Masliah, E.; Louis, E.D.; Faust, P.; Kang, U.J.; Torres, J.; Cortes, E.P.; Vonsattel, J.P.; Kuo, S.H.; Quinzii, C.M. Decreased coenzyme Q10 levels in multiple system atrophy cerebellum. *J. Neuropathol. Exp. Neurol.,* **2016**, *75*(7), 663-672. [http://dx.doi.org/10.1093/jnen/nlw037] [PMID: 27235405]

[28] Schottlaender, L.V.; Bettencourt, C.; Kiely, A.P.; Chalasani, A.; Neergheen, V.; Holton, J.L.; Hargreaves, I.; Houlden, H. Coenzyme Q10 Levels Are Decreased in the Cerebellum of Multiple-System Atrophy Patients. *PLoS One,* **2016**, *11*(2), e0149557. [http://dx.doi.org/10.1371/journal.pone.0149557] [PMID: 26894433]

[29] C. I.; Hyson, H. C.; Kieburtz, K.; Shoulson, I.; McDermott, M.; Ravina, B.; de Blieck, E. A.; Cudkowicz, M. E.; Ferrante, R. J.; Como, P.; Frank, S.; Zim-merman, C.; Cudkowicz, M. E.; Ferrante, K.; Newhall, K.; Jennings, D.; Kelsey, T.; Walker, F.; Hunt, V.; Daigneault, S.; Goldstein, M.; Weber, J.; Watts, A.; Beal, M. F.; Browne, S. E.; Metakis, L. J., Safety and tolerability of high-dosage coen-zyme Q10 in Huntington's disease and healthy subjects. *Mov. Disord.,* **2010**, *25*(12), 1924-1928. [PMID: 20669312]

[30] Emmanuele, V.; López, L.C.; Berardo, A.; Naini, A.; Tadesse, S.; Wen, B.; D'Agostino, E.; Solomon, M.; DiMauro, S.; Quinzii, C.; Hirano, M. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. *Arch. Neurol.,* **2012**, *69*(8), 978-983. [http://dx.doi.org/10.1001/archneurol.2012.206] [PMID: 22490322]

[31] Matsuda, Y.; Masahara, R. Photostability of solid-state ubidecarenone at ordinary and elevated temperatures under exaggerated UV irradiation. *J. Pharm. Sci.,* **1983**, *72*(10), 1198-1203. [http://dx.doi.org/10.1002/jps.2600721023] [PMID: 6644572]

[32] López, L.C.; Quinzii, C.M.; Area, E.; Naini, A.; Rahman, S.; Schuelke, M.; Salviati, L.; Dimauro, S.; Hirano, M. Treatment of CoQ(10) deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. *PLoS One,* **2010**, *5*(7), e11897. [http://dx.doi.org/10.1371/journal.pone.0011897] [PMID: 20689595]

[33] Suno, M.; Nagaoka, A. Inhibition of lipid peroxidation by a novel compound, idebenone (CV-2619). *Jpn. J. Pharmacol.,* **1984**, *35*(2), 196-198. [http://dx.doi.org/10.1254/jjp.35.196] [PMID: 6748380]

[34] Geromel, V.; Darin, N.; Chrétien, D.; Bénit, P.; DeLonlay, P.; Rötig, A.; Munnich, A.; Rustin, P.; Coenzyme, Q. Coenzyme Q(10) and idebenone in the therapy of respiratory chain diseases: rationale and comparative benefits. *Mol. Genet. Metab.,* **2002**, *77*(1-2), 21-30. [http://dx.doi.org/10.1016/S1096-7192(02)00145-2] [PMID: 12359126]

[35] Mordente, A.; Martorana, G.E.; Minotti, G.; Giardina, B. Antioxidant properties of 2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone (idebenone). *Chem. Res. Toxicol.,* **1998**, *11*(1), 54-63. [http://dx.doi.org/10.1021/tx970136j] [PMID: 9477226]

[36] Kutz, K.; Drewe, J.; Vankan, P. Pharmacokinetic properties and metabolism of idebenone. *J. Neurol.,* **2009**, *256*(Suppl. 1), 31-35. [http://dx.doi.org/10.1007/s00415-009-1006-z] [PMID: 19283348]

[37] Jaber, S.; Polster, B.M. Idebenone and neuroprotection: antioxidant, pro-oxidant, or electron carrier? *J. Bioenerg. Biomembr.,* **2015**, *47*(1-2), 111-118. [http://dx.doi.org/10.1007/s10863-014-9571-y] [PMID: 25262284]

[38] Yu-Wai-Man, P.; Soiferman, D.; Moore, D.G.; Burté, F.; Saada, A. Evaluating the therapeutic potential of idebenone and related quinone analogues in Leber hereditary optic neuropathy. *Mitochondrion,* **2017**, *36*, 36-42. [http://dx.doi.org/10.1016/j.mito.2017.01.004] [PMID: 28093355]

[39] Klopstock, T.; Metz, G.; Yu-Wai-Man, P.; Büchner, B.; Gallenmüller, C.; Bailie, M.; Nwali, N.; Griffiths, P.G.; von Livonius, B.; Reznicek, L.; Rouleau, J.; Coppard, N.; Meier, T.; Chinnery, P.F. Persistence of the treatment effect of idebenone in Leber's hereditary optic neuropathy. *Brain,* **2013**, *136*(Pt 2), e230. [http://dx.doi.org/10.1093/brain/aws279] [PMID: 23388409]

[40] Carelli, V.; La Morgia, C.; Valentino, M.L.; Rizzo, G.; Carbonelli, M.; De Negri, A.M.; Sadun, F.; Carta, A.; Guerriero, S.; Simonelli, F.; Sadun, A.A.; Aggarwal, D.; Liguori, R.; Avoni, P.; Baruzzi, A.; Zeviani, M.; Montagna, P.; Barboni, P. Idebenone treatment in Leber's hereditary optic neuropathy. *Brain,* **2011**, *134*(Pt 9), e188. [http://dx.doi.org/10.1093/brain/awr180] [PMID: 21810891]

[41] Imada, I.; Fujita, T.; Sugiyama, Y.; Okamoto, K.; Kobayashi, Y. Effects of idebenone and related compounds on respiratory activities of brain mitochondria, and on lipid peroxidation of their membranes. *Arch. Gerontol. Geriatr.,* **1989**, *8*(3), 323-341. [http://dx.doi.org/10.1016/0167-4943(89)90014-9] [PMID: 2764646]

[42] Brière, J.J.; Schlemmer, D.; Chretien, D.; Rustin, P. Quinone analogues regulate mitochondrial substrate competitive oxidation. *Biochem. Biophys. Res. Commun.,* **2004**, *316*(4), 1138-1142. [http://dx.doi.org/10.1016/j.bbrc.2004.03.002] [PMID: 15044103]

[43] Dinkova-Kostova, A.T.; Talalay, P. NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector. *Arch. Biochem. Biophys.,* **2010**, *501*(1), 116-123. [http://dx.doi.org/10.1016/j.abb.2010.03.019] [PMID: 20361926]

[44] Niki, E. Tocopherylquinone and tocopherylhydroquinone. *Redox Rep.,* **2007**, *12*(5), 204-210. [http://dx.doi.org/10.1179/135100007X200353] [PMID: 17925092]

[45] Hughes, P.E.; Tove, S.B. Synthesis of alpha-tocopherolquinone by the rat and its reduction by mitochondria. *J. Biol. Chem.,* **1980**, *255*(15), 7095-7097. [PMID: 7391070]

[46] Hawi, A.; Heald, S.; Sciascia, T. Use of an adaptive study design in single ascending-dose pharmacokinetics of A0001 (α-tocopherylquinone) in healthy male subjects. *J. Clin. Pharmacol.,* **2012**, *52*(1), 65-77. [http://dx.doi.org/10.1177/0091270010390807] [PMID: 21343342]

[47] Lynch, D.R.; Willi, S.M.; Wilson, R.B.; Cotticelli, M.G.; Brigatti, K.W.; Deutsch, E.C.; Kucheruk, O.; Shrader, W.; Rioux, P.; Miller, G.; Hawi, A.; Sciascia, T. A0001 in Friedreich ataxia: biochemical characterization and effects in a clinical trial. *Mov. Disord.,* **2012**, *27*(8), 1026-1033. [http://dx.doi.org/10.1002/mds.25058] [PMID: 22744651]

[48] Bidichandani, S.I.; Delatycki, M.B. Friedreich Ataxia.In GeneReviews(R)Seattle (WA), **1993**, 2018.

[49] Shrader, W.D.; Amagata, A.; Barnes, A.; Enns, G.M.; Hinman, A.; Jankowski, O.; Kheifets, V.; Komatsuzaki, R.; Lee, E.; Mollard, P.; Murase, K.; Sadun, A.A.; Thoolen, M.; Wesson, K.; Miller, G. α-Tocotrienol quinone modulates oxidative stress response and the biochemistry of aging. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(12), 3693-3698. [http://dx.doi.org/10.1016/j.bmcl.2011.04.085] [PMID: 21600768]

[50] Enns, G.M. Treatment of mitochondrial disorders: antioxidants and beyond. *J. Child Neurol.,* **2014**, *29*(9), 1235-1240. [http://dx.doi.org/10.1177/0883073814538509] [PMID: 24985754]

[51] Enns, G.M.; Kinsman, S.L.; Perlman, S.L.; Spicer, K.M.; Abdenur, J.E.; Cohen, B.H.; Amagata, A.; Barnes, A.; Kheifets, V.; Shrader, W.D.; Thoolen, M.; Blankenberg, F.; Miller, G. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. *Mol. Genet. Metab.,* **2012**, *105*(1), 91-102. [http://dx.doi.org/10.1016/j.ymgme.2011.10.009] [PMID: 22115768]

[52] Murphy, M.P.; Smith, R.A. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu. Rev. Pharmacol. Toxicol.,* **2007**, *47*, 629-656. [http://dx.doi.org/10.1146/annurev.pharmtox.47.120505.105110] [PMID: 17014364]

[53] Ross, M.F.; Kelso, G.F.; Blaikie, F.H.; James, A.M.; Cochemé, H.M.; Filipovska, A.; Da Ros, T.; Hurd, T.R.; Smith, R.A.; Murphy, M.P. Lipophilic triphenylphosphonium cations as tools in mitochondrial bioenergetics and free radical biology. *Biochemistry (Mosc.),* **2005**, *70*(2), 222-230. [http://dx.doi.org/10.1007/s10541-005-0104-5] [PMID: 15807662]

[54] Murphy, M.P. Understanding and preventing mitochondrial oxidative damage. *Biochem. Soc. Trans.,* **2016**, *44*(5), 1219-1226. [http://dx.doi.org/10.1042/BST20160108] [PMID: 27911703]

[55] Kelso, G.F.; Porteous, C.M.; Coulter, C.V.; Hughes, G.; Porteous, W.K.; Ledgerwood, E.C.; Smith, R.A.; Murphy, M.P. Selective targeting of a redox-active ubiquinone to mitochondria within cells: antioxidant and antiapoptotic properties. *J. Biol. Chem.,* **2001**, *276*(7), 4588-4596. [http://dx.doi.org/10.1074/jbc.M009093200] [PMID: 11092892]

[56] James, A.M.; Sharpley, M.S.; Manas, A.R.; Frerman, F.E.; Hirst, J.; Smith, R.A.; Murphy, M.P. Interaction of the mitochondria-targeted antioxidant MitoQ with phospholipid bilayers and ubiquinone oxidoreductases. *J. Biol. Chem.,* **2007**, *282*(20), 14708-14718. [http://dx.doi.org/10.1074/jbc.M611463200] [PMID: 17369262]

[57] Asin-Cayuela, J.; Manas, A.R.; James, A.M.; Smith, R.A.; Murphy, M.P. Fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant. *FEBS Lett.,* **2004**, *571*(1-3), 9-16. [http://dx.doi.org/10.1016/j.febslet.2004.06.045] [PMID: 15280009]

[58] Snow, B.J.; Rolfe, F.L.; Lockhart, M.M.; Frampton, C.M.; O'Sullivan, J.D.; Fung, V.; Smith, R.A.; Murphy, M.P.; Taylor, K.M. A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. *Mov. Disord.,* **2010**, *25*(11), 1670-1674. [http://dx.doi.org/10.1002/mds.23148] [PMID: 20568096]

[59] Wagner, K.H.; Kamal-Eldin, A.; Elmadfa, I. Gamma-tocopherol--an underestimated vitamin? *Ann. Nutr. Metab.,* **2004**, *48*(3), 169-188. [http://dx.doi.org/10.1159/000079555] [PMID: 15256801]

[60] Muller, D.P.; Harries, J.T.; Lloyd, J.K. The relative importance of the factors involved in the absorption of vitamin E in children. *Gut,* **1974**, *15*(12), 966-971. [http://dx.doi.org/10.1136/gut.15.12.966] [PMID: 4448411]

[61] Baydas, G.; Karatas, F.; Gursu, M.F.; Bozkurt, H.A.; Ilhan, N.; Yasar, A.; Canatan, H. Antioxidant vitamin levels in term and preterm infants and their relation to maternal vitamin status. *Arch. Med. Res.,* **2002**, *33*(3), 276-280. [http://dx.doi.org/10.1016/S0188-4409(02)00356-9] [PMID: 12031634]

[62] Ulatowski, L.; Parker, R.; Warrier, G.; Sultana, R.; Butterfield, D.A.; Manor, D. Vitamin E is essential for Purkinje neuron integrity. *Neuroscience,* **2014**, *260*, 120-129. [http://dx.doi.org/10.1016/j.neuroscience.2013.12.001] [PMID: 24342566]

[63] Cavalier, L.; Ouahchi, K.; Kayden, H.J.; Di Donato, S.; Reutenauer, L.; Mandel, J.L.; Koenig, M. Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. *Am. J. Hum. Genet.,* **1998**, *62*(2), 301-310. [http://dx.doi.org/10.1086/301699] [PMID: 9463307]

[64] Mardones, P.; Rigotti, A. Cellular mechanisms of vitamin E uptake: relevance in alpha-tocopherol metabolism and potential implications for disease. *J. Nutr. Biochem.,* **2004**, *15*(5), 252-260. [http://dx.doi.org/10.1016/j.jnutbio.2004.02.006] [PMID: 15135148]

[65] Borel, P.; Preveraud, D.; Desmarchelier, C. Bioavailability of vitamin E in humans: an update. *Nutr. Rev.,* **2013**, *71*(6), 319-331. [http://dx.doi.org/10.1111/nure.12026] [PMID: 23731443]

[66] Muller, D.P.; Lloyd, J.K.; Wolff, O.H. Vitamin E and neurological function. *Lancet,* **1983**, *1*(8318), 225-228. [http://dx.doi.org/10.1016/S0140-6736(83)92598-9] [PMID: 6130255]

[67] Muller, D.P. Vitamin E and neurological function. *Mol. Nutr. Food Res.,* **2010**, *54*(5), 710-718. [http://dx.doi.org/10.1002/mnfr.200900460] [PMID: 20183831]

[68] Nishimura, Y.; Hara, H. Integrated approaches to drug discovery for oxidative stress-related retinal diseases. *Oxid. Med. Cell. Longev.,* **2016**, *2016*, 2370252. [http://dx.doi.org/10.1155/2016/2370252] [PMID: 28053689]

[69] Wang, H.; O'Reilly, E.J.; Weisskopf, M.G.; Logroscino, G.; McCullough, M.L.; Schatzkin, A.; Kolonel, L.N.; Ascherio, A. Vitamin E intake and risk of amyotrophic lateral sclerosis: a pooled analysis of data from 5 prospective cohort studies. *Am. J. Epidemiol.,* **2011**, *173*(6), 595-602. [http://dx.doi.org/10.1093/aje/kwq416] [PMID: 21335424]

[70] Schuelke, M. Ataxia with Vitamin E Deficiency. In GeneReviews(R)Seattle (WA), **1993**, 2016.

[71] Loughrill, E.; Govinden, P.; Zand, N. Vitamins A and E content of commercial infant foods in the UK: A cause for concern? *Food Chem.,* **2016**, *210*, 56-62. [http://dx.doi.org/10.1016/j.foodchem.2016.04.014] [PMID: 27211620]

[72] Bahtouee, M.; Monavarsadegh, G.; Ahmadipour, M.; Motieilangroodi, M.; Motamed, N.; Saberifard, J.; Eghbali, S.; Adibi, H.; Maneshi, H.; Malekizadeh, H. Acetylcysteine in the treatment of subacute sinusitis: A double-blind placebo-controlled clinical trial. *Ear Nose Throat J.,* **2017**, *96*(1), E7-E11. [PMID: 28122105]

[73] Yoon, E.; Babar, A.; Choudhary, M.; Kutner, M.; Pyrsopoulos, N. Acetaminophen-induced hepatotoxicity: A comprehensive update. *J. Clin. Transl. Hepatol.,* **2016**, *4*(2), 131-142. [PMID: 27350943]

[74] Bavarsad Shahripour, R.; Harrigan, M.R.; Alexandrov, A.V. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. *Brain Behav.,* **2014**, *4*(2), 108-122. [http://dx.doi.org/10.1002/brb3.208] [PMID: 24683506]

[75] Huang, C.S.; He, W.; Meister, A.; Anderson, M.E. Amino acid sequence of rat kidney glutathione synthetase. *Proc. Natl. Acad. Sci. USA,* **1995**, *92*(4), 1232-1236. [http://dx.doi.org/10.1073/pnas.92.4.1232] [PMID: 7862666]

[76] Arakawa, M.; Ito, Y. N-acetylcysteine and neurodegenerative diseases: basic and clinical pharmacology. *Cerebellum,* **2007**, *6*(4), 308-314. [http://dx.doi.org/10.1080/14734220601142878] [PMID: 17853088]

[77] Giustarini, D.; Milzani, A.; Dalle-Donne, I.; Tsikas, D.; Rossi, R. N-Acetylcysteine ethyl ester (NACET): a novel lipophilic cell-permeable cysteine derivative with an unusual pharmacokinetic feature and remarkable antioxidant potential. *Biochem. Pharmacol.,* **2012**, *84*(11), 1522-1533. [http://dx.doi.org/10.1016/j.bcp.2012.09.010] [PMID: 23000913]

[78] Sunitha, K.; Hemshekhar, M.; Thushara, R.M.; Santhosh, M.S.; Yariswamy, M.; Kemparaju, K.; Girish, K.S. N-Acetylcysteine amide: a derivative to fulfill the promises of N-Acetylcysteine. *Free Radic. Res.,* **2013**, *47*(5), 357-367. [http://dx.doi.org/10.3109/10715762.2013.781595] [PMID: 23472882]

[79] Maddirala, Y.; Tobwala, S.; Ercal, N. N-acetylcysteineamide protects against manganese-induced toxicity in SHSY5Y cell line. *Brain Res.,* **2015**, *1608*, 157-166. [http://dx.doi.org/10.1016/j.brainres.2015.02.006] [PMID: 25681547]

[80] Halliwell, B.; Chirico, S. Lipid peroxidation: its mechanism, measurement, and significance *Am. J. Clin. Nutr.,* **1993**, *57*(5 Suppl)(), 715S-724S. discussion 724S-725S

[81] Alessandri, J.M.; Guesnet, P.; Vancassel, S.; Astorg, P.; Denis, I.; Langelier, B.; Aïd, S.; Poumès-Ballihaut, C.; Champeil-Potokar, G.; Lavialle, M. Polyunsaturated fatty acids in the central nervous system: evolution of concepts and nutritional implications throughout life. *Reprod. Nutr. Dev.,* **2004**, *44*(6), 509-538. [http://dx.doi.org/10.1051/rnd:2004063] [PMID: 15762297]

[82] Bayir, H.; Fadeel, B.; Palladino, M.J.; Witasp, E.; Kurnikov, I.V.; Tyurina, Y.Y.; Tyurin, V.A.; Amoscato, A.A.; Jiang, J.; Kochanek, P.M.; DeKosky, S.T.; Greenberger, J.S.; Shvedova, A.A.; Kagan, V.E. Apoptotic interactions of cytochrome c: redox flirting with anionic phospholipids within and outside of mitochondria. *Biochim. Biophys. Acta,* **2006**, *1757*(5-6), 648-659. [http://dx.doi.org/10.1016/j.bbabio.2006.03.002] [PMID: 16740248]

[83] Hill, S.; Lamberson, C.R.; Xu, L.; To, R.; Tsui, H.S.; Shmanai, V.V.; Bekish, A.V.; Awad, A.M.; Marbois, B.N.; Cantor, C.R.; Porter, N.A.; Clarke, C.F.; Shchepinov, M.S. Small amounts of isotope-reinforced polyunsaturated fatty acids suppress lipid autoxidation. *Free Radic. Biol. Med.,* **2012**, *53*(4), 893-906. [http://dx.doi.org/10.1016/j.freeradbiomed.2012.06.004] [PMID: 22705367]

[84] Cotticelli, M.G.; Crabbe, A.M.; Wilson, R.B.; Shchepinov, M.S. Insights into the role of oxidative stress in the pathology of Friedreich ataxia using peroxidation resistant polyunsaturated fatty acids. *Redox Biol.,* **2013**, *1*, 398-404. [http://dx.doi.org/10.1016/j.redox.2013.06.004] [PMID: 25499576]

[85] Lagier-Tourenne, C.; Tazir, M.; López, L.C.; Quinzii, C.M.; Assoum, M.; Drouot, N.; Busso, C.; Makri, S.; Ali-Pacha, L.; Benhassine, T.; Anheim, M.; Lynch, D.R.; Thibault, C.; Plewniak, F.; Bianchetti, L.; Tranchant, C.; Poch, O.; DiMauro, S.; Mandel, J.L.; Barros, M.H.; Hirano, M.; Koenig, M. ADCK3, an ancestral kinase, is mutated in a form of recessive ataxia associated with coenzyme Q10 deficiency. *Am. J. Hum. Genet.,* **2008**, *82*(3), 661-672. [http://dx.doi.org/10.1016/j.ajhg.2007.12.024] [PMID: 18319074]

[86] Mignot, C.; Apartis, E.; Durr, A.; Marques Lourenço, C.; Charles, P.; Devos, D.; Moreau, C.; de Lonlay, P.; Drouot, N.; Burglen, L.; Kempf, N.; Nourisson, E.; Chantot-Bastaraud, S.; Lebre, A.S.; Rio, M.; Chaix, Y.; Bieth, E.; Roze, E.; Bonnet, I.; Canaple, S.; Rastel, C.; Brice, A.; Rötig, A.; Desguerre, I.; Tranchant, C.; Koenig, M.; Anheim, M. Phenotypic variability in ARCA2 and identification of a core ataxic phenotype with slow progression. *Orphanet J. Rare*

Dis., **2013**, *8*(1), 173. [http://dx.doi.org/10.1186/1750-1172-8-173] [PMID: 24164873]

[87] Hikmat, O.; Tzoulis, C.; Knappskog, P.M.; Johansson, S.; Boman, H.; Sztromwasser, P.; Lien, E.; Brodtkorb, E.; Ghezzi, D.; Bindoff, L.A. ADCK3 mutations with epilepsy, stroke-like episodes and ataxia: a POLG mimic? *Eur. J. Neurol.,* **2016**, *23*(7), 1188-1194. [http://dx.doi.org/10.1111/ene.13003] [PMID: 27106809]

[88] Barca, E.; Musumeci, O.; Montagnese, F.; Marino, S.; Granata, F.; Nunnari, D.; Peverelli, L.; DiMauro, S.; Quinzii, C.M.; Toscano, A. Cerebellar ataxia and severe muscle CoQ10 deficiency in a patient with a novel mutation in ADCK3. *Clin. Genet.,* **2016**, *90*(2), 156-160. [http://dx.doi.org/10.1111/cge.12742] [PMID: 26818466]

[89] Liu, Y.T.; Hersheson, J.; Plagnol, V.; Fawcett, K.; Duberley, K.E.; Preza, E.; Hargreaves, I.P.; Chalasani, A.; Laurá, M.; Wood, N.W.; Reilly, M.M.; Houlden, H. Autosomal-recessive cerebellar ataxia caused by a novel ADCK3 mutation that elongates the protein: clinical, genetic and biochemical characterisation. *J. Neurol. Neurosurg. Psychiatry,* **2014**, *85*(5), 493-498. [http://dx.doi.org/10.1136/jnnp-2013-306483] [PMID: 24218524]

[90] Blumkin, L.; Leshinsky-Silver, E.; Zerem, A.; Yosovich, K.; Lerman-Sagie, T.; Lev, D. Heterozygous mutations in the ADCK3 gene in siblings with cerebellar atrophy and extreme phenotypic variability. *JIMD Rep.,* **2014**, *12*, 103-107. [http://dx.doi.org/10.1007/8904_2013_251] [PMID: 24048965]

[91] Acosta, M. J.; Vazquez Fonseca, L.; Desbats, M. A.; Cerqua, C.; Zordan, R.; Trevisson, E.; Salviati, L. Coenzyme Q biosynthesis in health and disease. *Biochim. Biophys. Acta,* **2016**, *1857*(8), 1079-85.

[92] Stefely, J.A.; Licitra, F.; Laredj, L.; Reidenbach, A.G.; Kemmerer, Z.A.; Grangeray, A.; Jaeg-Ehret, T.; Minogue, C.E.; Ulbrich, A.; Hutchins, P.D.; Wilkerson, E.M.; Ruan, Z.; Aydin, D.; Hebert, A.S.; Guo, X.; Freiberger, E.C.; Reutenauer, L.; Jochem, A.; Chergova, M.; Johnson, I.E.; Lohman, D.C.; Rush, M.J.P.; Kwiecien, N.W.; Singh, P.K.; Schlagowski, A.I.; Floyd, B.J.; Forsman, U.; Sindelar, P.J.; Westphall, M.S.; Pierrel, F.; Zoll, J.; Dal Peraro, M.; Kannan, N.; Bingman, C.A.; Coon, J.J.; Isope, P.; Puccio, H.; pagliarini, D.J. Cerebellar ataxia and coenzyme Q deficiency through loss of unorthodox kinase. *Mol. Cell,* **2016**, *63*(4), 608-620. [http://dx.doi.org/10.1016/j.molcel.2016.06.030] [PMID: 27499294]

[93] Ziosi, M.; Di Meo, I.; Kleiner, G.; Gao, X.H.; Barca, E.; Sanchez-Quintero, M.J.; Tadesse, S.; Jiang, H.; Qiao, C.; Rodenburg, R.J.; Scalais, E.; Schuelke, M.; Willard, B.; Hatzoglou, M.; Tiranti, V.; Quinzii, C.M. Coenzyme Q deficiency causes impairment of the sulfide oxidation pathway. *EMBO Mol. Med.,* **2017**, *9*(1), 96-111. [http://dx.doi.org/10.15252/emmm.201606356] [PMID: 27856618]

[94] Luna-Sánchez, M.; Díaz-Casado, E.; Barca, E.; Tejada, M.A.; Montilla-García, Á.; Cobos, E.J.; Escames, G.; Acuña-Castroviejo, D.; Quinzii, C.M.; López, L.C. The clinical heterogeneity of coenzyme Q10 deficiency results from genotypic differences in the Coq9 gene. *EMBO Mol. Med.,* **2015**, *7*(5), 670-687. [http://dx.doi.org/10.15252/emmm.201404632] [PMID: 25802402]

[95] García-Corzo, L.; Luna-Sánchez, M.; Doerrier, C.; Ortiz, F.; Escames, G.; Acuña-Castroviejo, D.; López, L.C. Ubiquinol-10 ameliorates mitochondrial encephalopathy associated with CoQ deficiency. *Biochim. Biophys. Acta,* **2014**, *1842*(7), 893-901. [http://dx.doi.org/10.1016/j.bbadis.2014.02.008] [PMID: 24576561]

[96] Ben, H.C.; Doerflinger, N.; Belal, S.; Linder, C.; Reutenauer, L.; Dib, C.; Gyapay, G.; Vignal, A.; Le Paslier, D.; Cohen, D. Localization of Friedreich ataxia phenotype with selective vitamin E deficiency to chromosome 8q by homozygosity mapping. *Nat. Genet.,* **1993**, *5*(2), 195-200. [http://dx.doi.org/10.1038/ng1093-195] [PMID: 8252047]

[97] El Euch-Fayache, G.; Bouhlal, Y.; Amouri, R.; Feki, M.; Hentati, F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. *Brain,* **2014**, *137*(Pt 2), 402-410. [http://dx.doi.org/10.1093/brain/awt339] [PMID: 24369383]

[98] Dürr, A.; Cossee, M.; Agid, Y.; Campuzano, V.; Mignard, C.; Penet, C.; Mandel, J.L.; Brice, A.; Koenig, M. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N. Engl. J. Med.,* **1996**, *335*(16), 1169-1175. [http://dx.doi.org/10.1056/NEJM199610173351601] [PMID: 8815938]

[99] Campuzano, V.; Montermini, L.; Moltò, M.D.; Pianese, L.; Cossée, M.; Cavalcanti, F.; Monros, E.; Rodius, F.; Duclos, F.; Monticelli, A.; Zara, F.; Cañizares, J.; Koutnikova, H.; Bidichandani, S.I.; Gellera, C.; Brice, A.; Trouillas, P.; De Michele, G.; Filla, A.; De Frutos, R.; Palau, F.; Patel, P.I.; Di Donato, S.; Mandel, J.L.; Cocozza, S.; Koenig, M.; Pandolfo, M. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science,* **1996**, *271*(5254), 1423-1427. [http://dx.doi.org/10.1126/science.271.5254.1423] [PMID: 8596916]

[100] Campuzano, V.; Montermini, L.; Lutz, Y.; Cova, L.; Hindelang, C.; Jiralerspong, S.; Trottier, Y.; Kish, S.J.; Faucheux, B.; Trouillas, P.; Authier, F.J.; Dürr, A.; Mandel, J.L.; Vescovi, A.; Pandolfo, M.; Koenig, M. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum. Mol. Genet.,* **1997**, *6*(11), 1771-1780. [http://dx.doi.org/10.1093/hmg/6.11.1771] [PMID: 9302253]

[101] Mariotti, C.; Solari, A.; Torta, D.; Marano, L.; Fiorentini, C.; Di Donato, S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology,* **2003**, *60*(10), 1676-1679. [http://dx.doi.org/10.1212/01.WNL.0000055872.50364.FC] [PMID: 12771264]

[102] Weidemann, F.; Rummey, C.; Bijnens, B.; Störk, S.; Jasaityte, R.; Dhooge, J.; Baltabaeva, A.; Sutherland, G.; Schulz, J.B.; Meier, T. The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. *Circulation,* **2012**, *125*(13), 1626-1634. [http://dx.doi.org/10.1161/CIRCULATIONAHA.111.059477] [PMID: 22379112]

[103] Cooper, J.M.; Korlipara, L.V.; Hart, P.E.; Bradley, J.L.; Schapira, A.H. Coenzyme Q10 and vitamin E deficiency in Friedreich's ataxia: predictor of efficacy of vitamin E and coenzyme Q10 therapy. *Eur. J. Neurol.,* **2008**, *15*(12), 1371-1379. [http://dx.doi.org/10.1111/j.1468-1331.2008.02318.x] [PMID: 19049556]

[104] Kearney, M.; Orrell, R.W.; Fahey, M.; Brassington, R.; Pandolfo, M. Pharmacological treatments for Friedreich ataxia. *Cochrane Database Syst. Rev.,* **2016**, (8), CD007791. [PMID: 27572719]

[105] Lynch, D.R.; Perlman, S.L.; Meier, T. A phase 3, double-blind, placebo-controlled trial of idebenone in friedreich ataxia. *Arch. Neurol.,* **2010**, *67*(8), 941-947. [http://dx.doi.org/10.1001/archneurol.2010.168] [PMID: 20697044]

[106] Bird, T.D. Hereditary Ataxia Overview. In GeneReviews(R), **1993**, 2016.

[107] Durr, A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *Lancet Neurol.,* **2010**, *9*(9), 885-894. [http://dx.doi.org/10.1016/S1474-4422(10)70183-6] [PMID: 20723845]

[108] Lo, R.Y.; Figueroa, K.P.; Pulst, S.M.; Lin, C.Y.; Perlman, S.; Wilmot, G.; Gomez, C.; Schmahmann, J.; Paulson, H.; Shakkottai, V.G.; Ying, S.; Zesiewicz, T.; Bushara, K.; Geschwind, M.; Xia, G.; Subramony, S.H.; Ashizawa, T.; Kuo, S.H. Coenzyme Q10 and spinocerebellar ataxias. *Mov. Disord.,* **2015**, *30*(2), 214-220. [http://dx.doi.org/10.1002/mds.26088] [PMID: 25449974]

[109] Stucki, D.M.; Ruegsegger, C.; Steiner, S.; Radecke, J.; Murphy, M.P.; Zuber, B.; Saxena, S. Mitochondrial impairments contribute to Spinocerebellar ataxia type 1 progression and can be ameliorated by the mitochondria-targeted antioxidant MitoQ. *Free Radic. Biol. Med.,* **2016**, *97*, 427-440. [http://dx.doi.org/10.1016/j.freeradbiomed.2016.07.005] [PMID: 27394174]

[110] Gatti, R.A.; Berkel, I.; Boder, E.; Braedt, G.; Charmley, P.; Concannon, P.; Ersoy, F.; Foroud, T.; Jaspers, N.G.; Lange, K. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. *Nature,* **1988**, *336*(6199), 577-580. [http://dx.doi.org/10.1038/336577a0] [PMID: 3200306]

[111] Maciejczyk, M.; Mikoluc, B.; Pietrucha, B.; Heropolitanska-Pliszka, E.; Pac, M.; Motkowski, R.; Car, H. Oxidative stress, mitochondrial abnormalities and antioxidant defense in Ataxia-telangiectasia, Bloom syndrome and Nijmegen breakage syndrome. *Redox Biol.,* **2017**, *11*, 375-383. [http://dx.doi.org/10.1016/j.redox.2016.12.030] [PMID: 28063379]

[112] Weyemi, U.; Redon, C.E.; Aziz, T.; Choudhuri, R.; Maeda, D.; Parekh, P.R.; Bonner, M.Y.; Arbiser, J.L.; Bonner, W.M. NADPH oxidase 4 is a critical mediator in Ataxia telangiectasia disease. *Proc. Natl. Acad. Sci. USA,* **2015**, *112*(7), 2121-2126. [http://dx.doi.org/10.1073/pnas.1418139112] [PMID: 25646414]

[113] Pagano, G.; Talamanca, A.A.; Castello, G.; Cordero, M.D.; d'Ischia, M.; Gadaleta, M.N.; Pallardó, F.V.; Petrović, S.; Tiano, L.; Zatterale, A. Oxidative stress and mitochondrial dysfunction across broad-ranging pathologies: toward mitochondria-targeted clinical strategies. *Oxid. Med. Cell. Longev.,* **2014**, *2014*, 541230. [http://dx.doi.org/10.1155/2014/541230] [PMID: 24876913]

[114] Reichenbach, J.; Schubert, R.; Schwan, C.; Müller, K.; Böhles, H.J.; Zielen, S. Anti-oxidative capacity in patients with ataxia telangiectasia. *Clin. Exp. Immunol.,* **1999**, *117*(3), 535-539. [http://dx.doi.org/10.1046/j.1365-2249.1999.01000.x] [PMID: 10469059]

[115] Degan, P.; d'Ischia, M.; Pallardó, F.V.; Zatterale, A.; Brusco, A.; Calzone, R.; Cavalieri, S.; Kavakli, K.; Lloret, A.; Manini, P.; Pisanti, M.A.; Vuttariello, E.; Pagano, G. Glutathione levels in blood from ataxia telangiectasia patients suggest *in vivo* adaptive mechanisms to oxidative stress. *Clin. Biochem.,* **2007**, *40*(9-10), 666-670. [http://dx.doi.org/10.1016/j.clinbiochem.2007.03.013] [PMID: 17466964]

[116] Reliene, R.; Schiestl, R.H. Experimental antioxidant therapy in ataxia telangiectasia. *Clin. Med. Oncol.,* **2008**, *2*, 431-436. [http://dx.doi.org/10.4137/CMO.S535] [PMID: 21892312]

[117] Date, H.; Onodera, O.; Tanaka, H.; Iwabuchi, K.; Uekawa, K.; Igarashi, S.; Koike, R.; Hiroi, T.; Yuasa, T.; Awaya, Y.; Sakai, T.; Takahashi, T.; Nagatomo, H.; Sekijima, Y.; Kawachi, I.; Takiyama, Y.; Nishizawa, M.; Fukuhara, N.; Saito, K.; Sugano, S.; Tsuji, S. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. *Nat. Genet.,* **2001**, *29*(2), 184-188. [http://dx.doi.org/10.1038/ng1001-184] [PMID: 11586299]

[118] Moreira, M.C.; Barbot, C.; Tachi, N.; Kozuka, N.; Uchida, E.; Gibson, T.; Mendonça, P.; Costa, M.; Barros, J.; Yanagisawa, T.; Watanabe, M.; Ikeda, Y.; Aoki, M.; Nagata, T.; Coutinho, P.; Sequeiros, J.; Koenig, M. The gene mutated in ataxia-ocular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. *Nat. Genet.,* **2001**, *29*(2), 189-193. [http://dx.doi.org/10.1038/ng1001-189] [PMID: 11586300]

[119] Castellotti, B.; Mariotti, C.; Rimoldi, M.; Fancellu, R.; Plumari, M.; Caimi, S.; Uziel, G.; Nardocci, N.; Moroni, I.; Zorzi, G.; Pareyson, D.; Di Bella, D.; Di Donato, S.; Taroni, F.; Gellera, C. Ataxia with oculomotor apraxia type1 (AOA1): novel and recurrent aprataxin mutations, coenzyme Q10 analyses, and clinical findings in Italian patients. *Neurogenetics,* **2011**, *12*(3), 193-201. [http://dx.doi.org/10.1007/s10048-011-0281-x] [PMID: 21465257]

[120] Gueven, N.; Becherel, O.J.; Kijas, A.W.; Chen, P.; Howe, O.; Rudolph, J.H.; Gatti, R.; Date, H.; Onodera, O.; Taucher-Scholz, G.; Lavin, M.F. Aprataxin, a novel protein that protects against genotoxic stress. *Hum. Mol. Genet.,* **2004**, *13*(10), 1081-1093. [http://dx.doi.org/10.1093/hmg/ddh122] [PMID: 15044383]

[121] Musumeci, O.; Naini, A.; Slonim, A.E.; Skavin, N.; Hadjigeorgiou, G.L.; Krawiecki, N.; Weissman, B.M.; Tsao, C.Y.; Mendell, J.R.; Shanske, S.; De Vivo, D.C.; Hirano, M.; DiMauro, S. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. *Neurology,* **2001**, *56*(7), 849-855. [http://dx.doi.org/10.1212/WNL.56.7.849] [PMID: 11294920]

[122] Sykora, P.; Croteau, D.L.; Bohr, V.A.; Wilson, D.M., III Aprataxin localizes to mitochondria and preserves mitochondrial function. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(18), 7437-7442. [http://dx.doi.org/10.1073/pnas.1100084108] [PMID: 21502511]

[123] Garcia-Diaz, B.; Barca, E.; Balreira, A.; Lopez, L.C.; Tadesse, S.; Krishna, S.; Naini, A.; Mariotti, C.; Castellotti, B.; Quinzii, C.M. Lack of aprataxin impairs mitochondrial functions *via* downregulation of the APE1/NRF1/NRF2 pathway. *Hum. Mol. Genet.,* **2015**, *24*(16), 4516-4529. [http://dx.doi.org/10.1093/hmg/ddv183] [PMID: 25976310]

[124] Gilman, S.; Wenning, G.K.; Low, P.A.; Brooks, D.J.; Mathias, C.J.; Trojanowski, J.Q.; Wood, N.W.; Colosimo, C.; Dürr, A.; Fowler, C.J.; Kaufmann, H.; Klockgether, T.; Lees, A.; Poewe, W.; Quinn, N.; Revesz, T.; Robertson, D.; Sandroni, P.; Seppi, K.; Vidailhet, M. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology,* **2008**, *71*(9), 670-676. [http://dx.doi.org/10.1212/01.wnl.0000324625.00404.15] [PMID: 18725592]

[125] Cykowski, M.D.; Coon, E.A.; Powell, S.Z.; Jenkins, S.M.; Benarroch, E.E.; Low, P.A.; Schmeichel, A.M.; Parisi, J.E. Expanding the spectrum of neuronal pathology in multiple system atrophy. *Brain,* **2015**, *138*(Pt 8), 2293-2309. [http://dx.doi.org/10.1093/brain/awv114] [PMID: 25981961]

[126] Fernagut, P.O.; Dehay, B.; Maillard, A.; Bezard, E.; Perez, P.; Pavy-Le Traon, A.; Rascol, O.; Foubert-Samier, A.; Tison, F.; Meissner, W.G. Multiple system atrophy: a prototypical synucleinopathy for disease-modifying therapeutic strategies. *Neurobiol. Dis.,* **2014**, *67*, 133-139. [http://dx.doi.org/10.1016/j.nbd.2014.03.021] [PMID: 24727096]

[127] Schottlaender, L.V.; Houlden, H. Mutant COQ2 in multiple-system atrophy. *N. Engl. J. Med.,* **2014**, *371*(1), 81. [PMID: 24988569]

[128] Multiple-system atrophy research collaboration. Mutations in COQ2 in familial and sporadic multiple-system atrophy. *N. Engl. J. Med.,* **2013**, *369*(3), 233-244. [http://dx.doi.org/10.1056/NEJMoa1212115] [PMID: 23758206]

[129] Sailer, A.; Scholz, S.W.; Nalls, M.A.; Schulte, C.; Federoff, M.; Price, T.R.; Lees, A.; Ross, O.A.; Dickson, D.W.; Mok, K.; Mencacci, N.E.; Schottlaender, L.; Chelban, V.; Ling, H.; O'Sullivan, S.S.; Wood, N.W.; Traynor, B.J.; Ferrucci, L.; Federoff, H.J.; Mhyre, T.R.; Morris, H.R.; Deuschl, G.; Quinn, N.; Widner, H.; Albanese, A.; Infante, J.; Bhatia, K.P.; Poewe, W.; Oertel, W.; Höglinger, G.U.; Wüllner, U.; Goldwurm, S.; Pellecchia, M.T.; Ferreira, J.; Tolosa, E.; Bloem, B.R.; Rascol, O.; Meissner, W.G.; Hardy, J.A.; Revesz, T.; Holton, J.L.; Gasser, T.; Wenning, G.K.; Singleton, A.B.; Houlden, H. A genome-wide association study in multiple system atrophy. *Neurology,* **2016**, *87*(15), 1591-1598. [http://dx.doi.org/10.1212/WNL.0000000000003221] [PMID: 27629089]

[130] Mitsui, J.; Matsukawa, T.; Yasuda, T.; Ishiura, H.; Tsuji, S. Plasma Coenzyme Q10 levels in patients with multiple system atrophy. *JAMA Neurol.,* **2016**, *73*(8), 977-980. [http://dx.doi.org/10.1001/jamaneurol.2016.1325] [PMID: 27356913]