Review

Friedreich’s ataxia: Coenzyme Q10 and vitamin E therapy

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Abstract

Since the identification of the genetic mutation causing Friedreich’s ataxia (FRDA) our understanding of the mechanisms underlying disease pathogenesis have improved markedly. The genetic abnormality results in the deficiency of frataxin, a protein targeted to the mitochondrion. There is extensive evidence that mitochondrial respiratory chain dysfunction, oxidative damage and iron accumulation play significant roles in the disease mechanism. There remains considerable debate as to the normal function of frataxin, but it is likely to be involved in mitochondrial iron handling, antioxidant regulation, and/or iron sulphur centre regulation. Therapeutic avenues for patients with FRDA are beginning to be explored in particular targeting antioxidant protection, enhancement of mitochondrial oxidative phosphorylation, iron chelation and more recently increasing FRDA transcription. The use of quinone therapy has been the most extensively studied to date with clear benefits demonstrated using evaluations of both disease biomarkers and clinical symptoms, and this is the topic that will be covered in this review.

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1. Clinical and pathological features

Friedreich’s ataxia (FRDA) usually presents in adolescence and clinical features include a progressive limb and gait ataxia, absence of deep tendon reflexes, extensor plantar responses, loss of position and vibration sense in the lower limbs and dysarthria. Hypertrophic cardiomyopathy and skeletal abnormalities (including scoliosis and pes cavus) are relatively common, while diabetes and optic atrophy also have an increased incidence (Harding, 1981; Durr et al., 1996). Following the identification of the genetic mutation of the FRDA gene in 1996 (Campuzano et al., 1996), patients with late onset (Bidichandani et al., 2000), retained reflexes (Klockgether et al., 1996), spastic paraplegia (Gates et al., 1998), pure sensory ataxia (Berciano et al., 1997) and chorea (Hanna et al., 1998) have been shown to have the genetic abnormality.

To date measurement of clinical progression in FRDA has been limited and while there are several clinical ratings scales for patients with ataxia, none have been specifically designed for FRDA although the international co-operative ataxia ratings scale (ICARS) (Trouillas et al., 1997) has been most widely used and validated (Cano et al., 2005). Several studies have compared the relationship between the genetic mutation and clinical presentation (Durr et al., 1996; Filla et al., 1996), but there has been very little detailed analysis of the natural history of FRDA and how different factors influence disease progression.

Pathologically the most obvious findings are loss of large sensory neurones in the dorsal root ganglia and deterioration of the sensory posterior and Clarke’s columns, spinocerebellar tracts and corticospinal motor tracts of the spinal cord (Harding, 1981). Cardiac hypertrophy is relatively common, and iron deposition in the heart has also been reported (Lamarche et al., 1993; Bradley et al., 2000).
2. Genetic features

FRDA is inherited in an autosomal recessive pattern with over 95% of patients having a homozygous expansion of a GAA triplet repeat in intron 1 of the FRDA gene on chromosome 9 (Campuzano et al., 1996). Normal alleles usually have between 6 and 34 GAA repeats which can be expanded to between 70 and 1700 in patients or carriers (Durr et al., 1996). Some patients are compound heterozygotes with the GAA expansion in one allele and one of a variety of point mutations in the other allele.

The FRDA gene encodes a protein containing 210 amino acids. The pathological GAA repeat expansions in intron 1 result in decreased frataxin mRNA leading to decreased frataxin protein levels in patients (Bidichandani et al., 1998; Wong et al., 1999). This is thought to be caused by the GAA/TTT repeats which have been shown to form unusual DNA structures, including DNA triplexes, leading to blockade of transcription (see review by Patel and Isaya, 2001). The size of the GAA repeat appears to influence the clinical phenotype with a significant inverse relationship between the size of the smaller GAA repeat and the age of onset (Durr et al., 1996). In agreement with the lower levels of frataxin mRNA, frataxin protein levels were decreased in proportion to the GAA repeat size, with frataxin level correlating with the size of the smallest GAA expansion in FRDA lymphoblasts (Campuzano et al., 1997). This supports the inverse relationship between GAA size and age of onset.

Analysis of the frataxin protein sequence failed to identify any similarities with domains in other proteins with known function. Frataxin has a predicted N-terminal mitochondrial targeting sequence and has been shown to reside within the mitochondrion (Campuzano et al., 1997), however the normal function of frataxin remains elusive. X-ray crystallography and functional studies indicate that frataxin may bind both proteins and iron (Dhe-Paganon et al., 2000; Yoon and Cowan, 2003; Bulteau et al., 2004) suggesting it may have a role in mitochondrial iron metabolism.

3. Models of FRDA

Disruption or knockout of the yeast frataxin homologue (YFH1) gene in several yeast models resulted in mitochondrial iron accumulation, impaired mitochondrial respiratory chain function, decreased mitochondrial DNA levels and an increased susceptibility to oxidative stress induced by hydrogen peroxide (Babcock et al., 1997; Koutnikova et al., 1997; Foury and Cazzalini, 1997). This is consistent with a role of the yeast frataxin homologue protein (yfh1p) in mitochondrial iron homeostasis, antioxidant defence mechanisms or mtDNA regulation.

Frataxin has an important role in development as knockout of frataxin is lethal at an early stage of embryological development, making mouse models of FRDA more difficult to generate. Two conditional gene targeting models gave rise to mice lacking a full length FRDA transcript in heart and skeletal muscle (MCK mice) or decreased levels in the brain, liver and kidney and absent level in the heart (NSE mice) (Puccio et al., 2001). Clinically the NSE mice expressed a rapidly progressive movement disorder from approx. 12 days while the MCK mice exhibited weight loss at 7 weeks followed by progressive signs of muscle fatigue. These models exhibited signs of cardiac hypertrophy, mitochondrial respiratory chain and aconitase dysfunction and iron accumulation (Puccio et al., 2001) but lacked evidence of oxidative damage (Seznec et al., 2005). This contrasted with a human frataxin YAC transgenic mouse model demonstrating neurodegeneration and cardiac iron deposition with increasing age, where oxidative damage was the main biochemical change (Al-Mahdawi et al., 2006).

4. Mitochondria, iron and oxidative stress in FRDA

Frataxin has clearly been shown to reside in the mitochondria, although there is now evidence of a small cytosolic pool of protein (Condo et al., 2006). In keeping with its mitochondrial location, deficiency of frataxin protein is associated with a decrease in mitochondrial respiratory chain complexes I, II and III and aconitase activities in post mortem heart and skeletal muscle from FRDA patients (Bradley et al., 2000).

$^{31}$P MRS analysis of FRDA patients has revealed markedly decreased oxidative phosphorylation in the heart (Lodi et al., 2001) and skeletal muscle, with the latter correlating with the size of the GAA1 repeat (Fig. 1, Lodi et al., 1999). These data underline the role of mitochondrial dysfunction in FRDA and suggest it is playing a primary role in disease pathogenesis.

The evidence of oxidative stress and damage in FRDA is quite extensive. It was first implicated when deficiency of the antioxidant vitamin E, caused by mutations of the alpha tocopherol transfer protein gene, was shown to cause a similar phenotype which responded to vitamin E therapy (AVED, Cavalier et al., 1998). As mitochondria have a very high vitamin E content (Buttriss and Diplock, 1988), and deficiency leads to impaired respiratory chain function (Thomas et al., 1993), it has been suggested that increased oxidative damage to the mitochondria may be the common mechanism between AVED and FRDA.

Various markers have indicated increased oxidative stress and damage in FRDA patients including; raised urine levels of 8-hydroxy-2'-deoxyguanosine (8OH2'dG)
suggesting elevated oxidative damage to DNA; decreased free glutathione levels in blood suggesting extensive glutathionylation of proteins in response to oxidative stress (Piemonte et al., 2001) and raised plasma malondialdehyde (MDA) levels indicative of increased lipid peroxidation (Emond et al., 2000; Bradley et al., 2004). The analysis of fibroblasts from FRDA patients suggests frataxin deficiency leads to a delayed antioxidant defence response, (Jiralerspong et al., 2001) which may relate to the increased sensitivity to free radical generation in yeast YFH1 knockout models and cultured fibroblasts from FRDA patients (Babcock et al., 1997; Bradley et al., 2004).

In agreement with the accumulation of mitochondrial iron in yeast YFH1 knockout models iron deposits have been detected in heart and liver from some but not all FRDA patients (Bradley et al., 2000; Lamarche et al., 1993). Consequently, rather than reflecting the antioxidant capacity of the cells it is possible that the increased sensitivity to oxidative stress in FRDA models reflects an increased mitochondrial labile iron content promoting Fenton chemistry and ensuing cell damage.

5. Disease mechanisms

The presence of increased mitochondrial iron, decreased respiratory chain activity and oxidative damage are common features in yeast and mouse models of frataxin deficiency and samples from FRDA patients. The primary role of frataxin and the primary consequences of its deficiency remain unresolved, however, there are important clues that are helping to delineate the chronology of these events.

The pattern of respiratory chain dysfunction in FRDA is reminiscent of that observed in situations where oxidative stress has been implicated including a manganese superoxide dismutase knockout transgenic mouse model (Melov et al., 1999), and Huntington’s disease (Tabrizi et al., 2000). Consistent with the idea that frataxin deficiency leads to increased mitochondrial iron levels and subsequent oxidative damage and mitochondrial respiratory chain dysfunction, chelating iron in the medium of yeast cells lacking yfh1p prevented mitochondrial iron accumulation and improved respiratory chain activities (Foury, 1999). This suggested that the mitochondrial iron accumulation was responsible for the decrease in respiratory chain function but the continued decrease in aconitase activity implied an alternative cause of the aconitase inhibition. This primary role of oxidative damage in FRDA contrasts with the lack of oxidative stress and damage markers in the MCK and NSE conditional mouse models (Seznec et al., 2005). This may reflect the focal loss of frataxin where the oxidative damage may be more restricted and less easily detected, or alternatively suggests the oxidative damage is a secondary response and requires the presence of residual frataxin levels. The presence of oxidative damage as the main biochemical consequence of decreased frataxin levels in another mouse model (Al-Mahdawi et al., 2006) also raises doubt about the significance of this feature of the conditional models.

Mitochondria play a pivotal role in cellular iron handling. With iron sulphur (Fe–S) centre (Lill et al., 1999) and haem biosynthesis pathways located within the mitochondrion, iron uptake needs to be tightly regulated in line with these processes. The increase in mitochondrial iron in the various models of FRDA and in patient samples is consistent with a role of frataxin in iron handling. The pattern of deficiency in FRDA involving Fe–S containing activities (complexes I–III and aconitase), while sparing cytochrome oxidase activity (which contains haem), was consistent with an abnormality of Fe–S centre but not haem synthesis. The proposed role of frataxin in Fe–S centre synthesis (Duby et al., 2002) is consistent with the secondary accumulation of mitochondrial iron which has also been reported in yeast mutants with defective iron sulphur synthesis (Kispal et al., 1997; Lange et al., 2000; Li et al., 1999; Knight et al., 1998).
In addition to a possible interaction with components of the Fe–S synthesis machinery (Yoon and Cowan, 2003; Stehling et al., 2004) more specific roles for frataxin have been suggested following interactions between frataxin and succinate dehydrogenase (Gonzalez-Cabo et al., 2004), aconitase (Bulteau et al., 2005), or aconitase (Bulteau et al., 2004) where it may have a regulatory role.

While the exact pathological mechanisms of FRDA are not understood there are a number of ways the biochemical abnormalities observed in FRDA can interact. Mitochondrial iron levels may increase due to decreased Fe–S synthesis leading to increased sensitivity to oxidative stress. Aconitase is an iron sulphur protein whose activity is particularly sensitive to free radical damage (Hausladen and Fridovich, 1994), consequently the decreased aconitase activities reported in heart and skeletal muscle from FRDA patients (Bradley et al., 2000; Rotig et al., 1997) may reflect elevated free radical damage and/or decreased Fe–S centre synthesis or repair. Likewise if Fe–S centre synthesis is impaired the resulting decrease in respiratory chain function could lead to elevated free radical generation and oxidative stress (Hasegawa et al., 1990).

While the exact role frataxin plays in the mitochondrion remains elusive, mitochondrial respiratory chain dysfunction, oxidative stress and iron accumulation appear to be exacerbated with disease progression, and are therefore useful targets for therapeutic intervention.

6. Coenzyme Q10 and vitamin E in ataxia

Coenzyme Q10 (CoQ10) and vitamin E are important mitochondrial antioxidants and deficiencies of both have been implicated in ataxia. Decreased muscle CoQ10 levels were reported in patients with genetically undefined cerebellar ataxia, (Lamperti et al., 2003) suggesting CoQ10 depletion may be a secondary phenomenon in diseases involving ataxia. In another study ICARS scores for patients with ataxia associated with a severe muscle CoQ10 deficiency improved after 1 year of oral CoQ10 therapy suggesting it played a significant role in pathogenesis and was responsive to therapy (Musumeci et al., 2001). Vitamin E is obtained solely from the diet and vitamin E deficiency caused by mutation of the alpha tocopherol transferring protein leads to ataxia (Ouahchi et al., 1995) which is responsive to vitamin E therapy (Kayden, 1993).

7. Therapeutic intervention

When approaching the issue of therapeutic intervention in a slowly progressive neurodegenerative disorder like FRDA there are many issues to consider including; type of therapy, whether any clinical effect will be restricted to modifying disease progression, the natural rate of clinical deterioration and therefore the duration of therapy required to show any benefit. The choice of therapy has predominantly been based upon what is understood about the disease mechanisms and the ability of the therapy to gain access to neurological tissues. Consequently therapeutic intervention has focussed on iron chelation, antioxidant protection and mitochondrial energy enhancement.

FRDA is associated with both neurological and non-neurological symptoms. The former are associated with neuronal loss and so therapy is only likely to slow their progression, other symptoms however, may demonstrate improvement with therapeutic intervention. The paucity of data relating to the validation of rating scales for the assessment of FRDA patients and also a lack of validated natural history data to predict disease progression has led to variations in trial design. Published trials have usually been open label trials with durations ranging between 6 months and 4 years and assessing clinical progression using ICARS, echocardiography and occasionally using 31P MRS as a biomarker of mitochondrial bioenergetics.

8. Antioxidant therapy

8.1. Idebenone

Idebenone is an analogue of coenzyme Q10 with a short isoprene side chain, it is well tolerated by humans, crosses the blood brain barrier (Nagai et al., 1989), has been reported to be a relatively good antioxidant (Mordente et al., 1998), and has been used in a variety of diseases with some benefits (Gutzmann and Hadler, 1998; Ranen et al., 1996). Idebenone therapy decreased the cardiac hypertrophy (as determined by echocardiography) in the majority of patients (Hausse et al., 2002) but there was no influence upon clinical progression (ICARS) (Hausse et al., 2002; Mariotti et al., 2003). Another assessment of idebenone failed to identify improvements in skeletal muscle bioenergetics (31P MRS) or echocardiographic parameters (Schols et al., 2001), although this may reflect the short time scale used.

9. Prolonged vitamin E and CoQ10 therapy

Vitamin E is a naturally occurring lipid soluble antioxidant distributed throughout cellular membranes but predominantly in mitochondrial membranes. It is obtained in the diet and vegetable oils and nuts provide a particularly rich source. Vitamin E treatment has been shown to increase vitamin E levels in a variety of tissues including brain, muscle and heart (Zhang et al., 1995). It has been used to treat cardiovascular disease, Parkinson’s disease, cancers and AVED with varying degrees of success (Stephens et al., 1996; Shoulson, 1998; Bostick et al., 1993; Gabsi et al., 2001), however, in FRDA its efficacy has only been assessed in conjunction with coenzyme Q10.

As mitochondrial respiratory chain dysfunction is a common feature in FRDA patients and various model systems, drugs which enhance mitochondrial ATP synthesis are good candidates for therapeutic intervention. As an electron carrier in the respiratory chain CoQ10 has been used to enhance cellular energy status. While CoQ10 is

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obtained in the diet it is also synthesised in all cells via a pathway that shares some of the steps involved in cholesterol biosynthesis. CoQ10 is readily taken up into the blood (Folkers et al., 1994), the brain (Matthews et al., 1998) and liver (Zhang et al., 1995) although other reports suggest dietary CoQ10 levels do not influence tissue CoQ10 levels in the rat (Reahal and Wrigglesworth, 1992). It is interesting to note that in rats fed two different doses of CoQ10 for varying lengths of time it was the duration of the diet rather than the dose of CoQ10 that was the most important variable when predicting the increase in tissue CoQ10 levels (Sohal et al., 2006).

CoQ10 has been beneficial in several neurological diseases including Parkinson’s disease (Schulz et al., 2000) and ataxia associated with markedly decreased CoQ10 levels (Musumeci et al., 2001). CoQ10 is believed to be involved in the reduction of oxidised vitamin E and therefore when combined in a therapy they may act synergistically (Ernster and Dallner, 1995). This was found to be the case in protecting rats against atherosclerosis (Thomas et al., 2001).

The combination of CoQ10 and vitamin E has been shown to be well tolerated and therefore is ideal for a long term study of a high dose therapy for FRDA. A 4 year open label trial has been completed with 10 genetically confirmed FRDA patients given 2100 IU/day vitamin E and 400 mg/day CoQ10 (Hart et al., 2005) and the data will be reviewed here. The International Cooperative Ataxia Ratings Scale was used to evaluate clinical progression, in addition to biomarkers of in vivo mitochondrial bioenergetics (cardiac and skeletal muscle 31P MRS) and cardiac hypertrophy (echocardiography) to evaluate the effect of therapy. During the course of the therapy all patients demonstrated an increase in serum vitamin E (2.2–6-fold increase over baseline) and CoQ10 levels (2.3–7.4-fold increase over baseline), (Fig. 2) demonstrating good bioavailability. Most remarkable was the improvement in cardiac (phosphocreatine:ATP ratio) and skeletal muscle (post exercise maximum rate of mitochondrial ATP synthesis, Vmax) bioenergetics after 3 months of therapy which was maintained throughout the 4 years of the trial (Hart et al., 2005). This clearly demonstrated that the combined vitamin E and CoQ10 therapy had a significant and prolonged benefit upon the defective mitochondrial function in these peripheral tissues. While the prolonged improvement in cardiac bioenergetics did not have any impact upon cardiac hypertrophy, fractional shortening (FS) showed a progressive improvement that reached significance after 3 years (Hart et al., 2005).

In the absence of a direct evaluation of mitochondrial function in neurological tissues changes to the patients’ ICARS scores were the only markers of neurological function. The clinical scores did not increase over the 4 years of the trial suggesting the disease progression was stabilised (Hart et al., 2005). A closer analysis of the component scores of the ICARS revealed that the posture and gait subscores increased significantly from the pre-therapy scores indicating clinical progression of these symptoms, while the kinetic subscores decreased (Hart et al., 2005), although not statistically significant, indicating clinical improvement.

Interpretation of the clinical data from a trial such as this one is complicated because patients with FRDA are a heterogeneous group with variables including age, disease onset, disease duration, GAA repeat size, clinical presentation and severity. This is not only reflected in the variable presentation at the beginning of the trial but will also influence their disease progression. When combined with a lack of comprehensive natural history data interpretation of a small trial like this one is quite difficult. To address this disease progression was predicted using cross-sectional data from 77 FRDA patients divided into four groups according to their GAA1 repeat size to account for the influence of
genetic severity on disease progression. The rate of clinical change for each patient over the 4 years of the trial was determined and compared with those predicted for the appropriate cross-sectional group. The change in clinical symptoms (total ICARS scores) were better than predicted in six patients and indeed demonstrated an improvement (Fig. 3). When the different components of this score were analysed it was clear that the kinetic scores paralleled those for the total ICARS scores, with the same six patients demonstrating an improvement and an additional patient with a more stable clinical picture than predicted, but the change in posture and gait scores were similar to the predicted scores for all except one patient who showed an improvement implying not all symptoms responded to this therapy (Hart et al., 2005).

Decreased energy supply appears to be an important early event in FRDA (Lodi et al., 1999). The improved cardiac and skeletal muscle MRS data clearly demonstrated that the therapy caused a sustained improvement in heart bioenergetics. While this was associated with improved fraction shortening there was no impact upon the degree of hypertrophy evident before therapy was started. However, little is documented about the natural history of the cardiac hypertrophy in FRDA and therefore it was not possible to determine if the therapy prevented progression of the hypertrophy. While there is some debate as to the effect of increased dietary CoQ10 and vitamin E upon tissue levels of these chemicals (Bhagavan and Chopra, 2006; Ibrahim et al., 2000) the improved heart and skeletal muscle 31P MRS features implies they are at least effectively targeting these tissues and had an influence upon clinical progression in at least a proportion of patients.

The lack of apparent benefit of CoQ10/vitamin E therapy on cardiac hypertrophy contrasted with that reported for idebenone therapy (Hausse et al., 2002; Mariotti et al., 2003; Buyse et al., 2003). This may relate to differences in patient selection, in particular the degree of cardiac hypertrophy prior to therapy was relatively mild in the vitamin E/CoQ10 study, alternatively the tissue penetration of the agents may differ. The differences did not relate to bioenergetic improvement as in contrast to this therapy, idebenone did not enhance oxidative phosphorylation (Schols et al., 2001). Conversely, the apparent clinical benefits of the CoQ10/vitamin E therapy, which have not been reported for idebenone therapy, may be related to the improvements in bioenergetics.

10. Conclusion

In conclusion, there is still some debate as to the exact pathological mechanisms involved in FRDA. However, the involvement of defective mitochondrial energetics and increased oxidative damage is widely accepted. The use of a high dose quinone therapy, either Idebenone or CoQ10 plus vitamin E have been shown to have clinical benefits. In particular Idebenone has decreased the cardiac hypertrophy and CoQ10 plus vitamin E caused a prolonged improvement in cardiac and skeletal muscle bioenergetics and clinical scores were improved in 7 out of 10 patients. Larger randomised controlled trials with improved longitudinal data are required to confirm the findings of these trials and to help interpret the benefits of these therapies in a wider population of patients.

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