

# Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia

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**Background:** Friedreich's ataxia encodes a protein of unknown function, frataxin. The loss of frataxin is caused by a large GAA trinucleotide expansion in the first intron of the gene, resulting in deficiency of a Krebs cycle enzyme, aconitase, and of three mitochondrial respiratory chain complexes (I-III). This causes oxidative stress. Idebenone, a short chain quinone acting as an antioxidant, has been shown to protect heart muscle against oxidative stress in some patients.

**Objective:** To assess the efficiency of idebenone on cardiac hypertrophy in Friedreich's ataxia.

**Design:** Prospective, open trial.

**Setting:** Tertiary care centre.

**Methods:** Idebenone (5 mg/kg/day) was given orally to 38 patients with Friedreich's ataxia aged 4-22 years (20 males, 18 females). Cardiac ultrasound indices were recorded before and after idebenone treatment.

**Results:** After six months, cardiac ultrasound indicated a reduction in left ventricular mass of more than 20% in about half the patients ( $p < 0.001$ ). The shortening fraction was initially reduced in six of the 38 patients (by between 11-26%) and it improved in five of these. In one patient, the shortening fraction only responded to 10 mg/kg/day of idebenone. No correlation was found between responsiveness to idebenone and age, sex, initial ultrasound indices, or the number of GAA repeats in the frataxin gene.

**Conclusions:** Idebenone is effective at controlling cardiac hypertrophy in Friedreich's ataxia. As the drug has no serious side effects, there is a good case for giving it continuously in a dose of 5-10 mg/kg/day in patients with Friedreich's ataxia at the onset of hypertrophic cardiomyopathy.

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Friedreich's ataxia is a degenerative disease characterised by progressive limb and gait ataxia, areflexia, pyramidal signs in the legs, and life threatening cardiomyopathy.<sup>1,2</sup> Both hypertrophic (concentric or asymmetric) and dilated cardiomyopathy have been reported.<sup>1,2</sup> It has been shown in a recent study that most patients who develop hypokinetic dilated cardiomyopathy originally had a hypertrophic left ventricle.<sup>3</sup> The gene causing this autosomal recessive condition maps to chromosome 9q13-q21.1 and encodes a 210 amino acid protein of unknown function, frataxin.<sup>4,5</sup> A large expansion of GAA trinucleotide repeats located in the first intron of the gene is detected in more than 90% of typical patients with Friedreich's ataxia.<sup>6,7</sup> A study of endomyocardial biopsies in patients with this disease who present with concentric hypertrophic cardiomyopathy,<sup>8</sup> and of yeast strains with deletion of the frataxin homologue gene, has revealed that the loss of frataxin causes oxidative stress with a combined deficiency of a Krebs cycle enzyme, aconitase, and three mitochondrial respiratory chain complexes (complexes I to III), together with a disturbance of cell iron homeostasis leading to mitochondrial iron overload.<sup>9-11</sup> Both respiratory chain dysfunction and oxidative stress are likely to result in cardiac or cardiomyocyte hypertrophy. Indeed, inherited respiratory chain diseases are often associated with hypertrophic cardiomyopathy, while disruption of the Tfam gene, necessary for mitochondrial DNA maintenance in the mouse, leads to a severe respiratory chain dysfunction and the thickening of the heart walls, followed by heart dilatation.<sup>12,13</sup> Moreover, inhibition of the cytosolic copper-zinc superoxide dismutase has recently been shown to induce cell hypertrophy in rat cardiac myocytes in vitro.<sup>14</sup> This suggests that either respiratory chain dysfunction or oxidative stress can trigger hypertrophic cardiomyopathy.

We have recently observed that idebenone, a short chain analogue of CoQ<sub>10</sub> that acts as a potent free radical scavenger,<sup>15</sup> protected heart muscle from iron injury in three patients with Friedreich's ataxia.<sup>16</sup> As idebenone has been shown to reduce cardiac hypertrophy in these patients, we have studied the factors that might determine the effect of idebenone on left ventricular mass and function in a larger series of patients with Friedreich's ataxia. We show that idebenone controls cardiac hypertrophy in such patients regardless of the size of the GAA expansion and the initial ultrasound indices.

## METHODS

We studied 38 patients with Friedreich's ataxia, aged 4-22 years (20 males, 18 females), with the informed consent of their parents where necessary. The diagnosis of Friedreich's ataxia was based on the detection on both alleles of a large GAA expansion in the first intron of the frataxin gene. Asymmetrical hypertrophic cardiomyopathy was observed in 10 patients and concentric hypertrophy in the others. No patient had dilated cardiomyopathy.

The patients were given idebenone orally (5 mg/kg daily during meals) over a six month period. Blood pressure was normal in all patients. Cardiac ultrasound indices were recorded immediately before and after six months of oral idebenone by the same ultrasonographer. Three ultrasonographers carried out the assessment, using an Accuson XP 128 machine (Accuson Inc, Mountain View, California, USA). Shortening fraction, septal thickness, and left ventricular posterior wall thickness were measured in M mode on parasternal, longitudinal, and transverse views, according to the recommendations of the committee on M mode standardisation of the American Society of Echocardiography.<sup>17</sup> Left

**Table 1** Effect of oral treatment with idebenone for six months on cardiac indices in Friedreich's ataxia

Patient number	Sex	Age (years)	Before treatment			After treatment			
			LV mass index (g/m <sup>2</sup> )	IVSd thickness (mm)	Shortening fraction (%)	LV mass index (g/m <sup>2</sup> )	IVSd thickness (mm)	Shortening fraction (%)	LV mass index change (%)
1	F	12	218	13	60	132	10	47	-39
2	F	11	154	15	37	99	9	40	-36
3	F	22	191	21	50	125	15	37	-35
4	M	12	364	17	46	237	11	54	-35
5	F	7	165	12	44	112	11	39	-32
6	M	17	121*	12	40	85*	8	36	-30
7	F	10	230	16	47	167	13	43	-28
8	M	10	170	14	52	126	10	49	-26
9	F	13	128	16	47	95	11	49	-26
10	M	4	202	13	38	154	12	51	-24
11	M	13	212	16	37	160	13	32	-24
12	M	22	178	17	11	135	13	23	-24
13	F	29	73	11	41	56	8	31	-23
14	M	14	101	10	50	79	9	47	-22
15	M	13	201	16	40	156	14	42	-22
16	M	6	240	14	25	189	10	20	-21
17	F	12	200	17	47	160	13	57	-20
18	F	13	130	10	32	105	9	32	-19
19	M	12	97	12	40	79	9	35	-18
20	M	31	113	14	26	94	12	51	-17
21	F	13	78	9	37	67	8	50	-14
22	M	8	286	16	51	245	17	51	-14
23	F	19	141	15	44	123	12	59	-13
24	F	12	146	12	45	131	11	39	-11
25	M	21	87	10	41	80	11	39	-8
26	F	20	130	12	47	119	12	47	-8
27	F	18	378	30	43	350	30	44	-7
28	M	17	113	10	37	106	10	47	-6
29	M	17	143*	9	31	137*	9	31	-5
30	M	10	248	15	25	237	10	30	-4
31	M	14	177	12	38	174	9	37	-1
32	M	18	131	12	34	132	11	36	+1
33	F	13	169	14	25	172	16	37	+2
34	F	21	121	10	47	128	15	43	+6
35	M	17	89	9	30	98	8	30	+10
36	M	9	358	18	23	392	17	14	+10
37	F	21	77	7	42	91	9	38	+18
38	F	15	93	11	45	109	10	37	+18
n=38; M/F ratio 1:1			Normal value: 80 (20) g/m <sup>2</sup>	Normal value: 33 (3)%		-14 (14) (p<0.001)†			

Normal values are given as mean (SD).  
 \*Left ventricular mass (g) not corrected for body surface.  
 †p Value associated with paired testing of left ventricular mass index before and after treatment.  
 F, female; IVSd thickness, interventricular septal thickness measured in diastole; LV, left ventricular; M, male.

ventricular mass was calculated according to Devereux and Reichek.<sup>18</sup> Of the six patients with a hypokinetic left ventricle, four were receiving angiotensin converting enzyme inhibitors. Two patients were on  $\beta$  adrenergic antagonists for left ventricular outflow obstruction before inclusion in the protocol. These treatments were continued unchanged during the six months of the trial.

We took the decision to perform an open trial rather than a double blind, placebo controlled study for the following reasons. We already had some evidence that idebenone, which is known to be safe, potentially reduces the life threatening heart disease in Friedreich's ataxia.<sup>16</sup> In the difficult context of a lethal disease with no cure, we therefore thought that it would have been unethical to withhold the drug. Friedreich's ataxia is a progressive disease with consistent (although variable) worsening and without any chance of recovery. Thus any measurable reversal of the pathology should be considered highly significant. This is particularly true of any decrease in cardiac hypertrophy, which obviously has very little likelihood of resulting from a placebo effect. Finally, except for a consistent tendency to worsen, the course of the disease differs greatly between individuals and this makes it difficult to have confidence in a control group unless it includes a very large number of patients—a requirement not easy to fulfil with this

rare disease. Thus, for both ethical and scientific reasons (that is, a trial of a safe drug in a disease which progresses inexorably towards death with no available cure), we took the decision to perform an open trial.

#### Statistical analysis

Paired testing was used (paired *t* test) to analyse the differences in heart measurements before and after six months of idebenone treatment.

#### RESULTS

After six months of idebenone treatment, a reduction in left ventricular mass of more than 20% was observed in half the patients (patients 1–17; table 1). The reduction in left ventricular mass index was highly significant (mean (SD), -27 (6)%; *p* < 0.001). Cardiac hypertrophy was largely stabilised in the remaining patients (patients 18–38), and in none did the hypertrophy increase by more than 20% over the six month period of the trial.

Obstruction to the left ventricular outflow tract was originally noted in two patients (3 and 10). This decreased notably after six months of idebenone administration, so that  $\beta$  adrenergic antagonists could be discontinued. The gradient pressure fell from 60 and 40 mm Hg to 30 and 10 mm Hg in



**Figure 1** Correlation of left ventricular mass index change with age (A), initial left ventricular mass index (B), and expansion size on the smaller allele of the frataxin gene (C).

patients 3 and 20, respectively, as determined by Doppler flow velocity measurements.

A reduced shortening fraction (11–26%, normal mean 33 (3)%) was originally observed in six of the 38 patients (12, 16, 20, 30, 33, 36; table 1) and improved in five after idebenone. The shortening fraction continued to deteriorate in patient 36, and because of the absence of side effects of idebenone,<sup>19</sup> this patient was given an increased dose of 10 mg/kg/day for an additional six months. This resulted in a decrease in the left ventricular mass index (from 392 to 210 g/m<sup>2</sup>; –46%) and a significant improvement in the shortening fraction (from 14% to 24%). The improvement of the shortening fraction in patients 30 and 33 was not associated with any significant change in myocardial mass.

We attempted to correlate the response to idebenone with the number of the GAA repeats of the smaller allele in the frataxin gene, and the stage of cardiac disease, based on the initial ultrasound findings (fig 1). Change in left ventricular mass index was not correlated with either of these two variables.

Finally, we did not find any significant correlation between either the age or the sex of the patient and the responsiveness of cardiac hypertrophy to idebenone (fig 1; table 1). Patients with asymmetrical and concentric hypertrophic cardiomyopathy responded equally to idebenone administration (table 1).

In the absence of an available validated rating scale, ataxia was not quantified. However, in none of the patients did the degree of ataxia or the deep tendon reflexes change noticeably over the six month period of idebenone treatment. In several

patients, parents or teachers noted a reduction in general weakness, an improvement in strength and in fine movements (for example, handwriting), more fluent speech, and a decrease in swallowing difficulties, suggesting that the beneficial effect of idebenone may not be restricted to the heart.

No particular side effects of the drug were noted in our series over the six month period, but some parents mentioned an increase in appetite and weight gain. These are only preliminary indications that the drug effect may not be limited to cardiac function, and they obviously require quantitative and controlled assessment.

## DISCUSSION

Friedreich's ataxia results from the loss of function of frataxin, a mitochondrial protein of hitherto unknown biological activity.<sup>20</sup> Frataxin deficient cells undergo oxidative stress and show generalised deficiency of iron sulphur proteins, with mitochondrial iron overload.<sup>8–11</sup> For this reason, idebenone—a short chain homologue of ubiquinone, previously shown to counteract iron induced injury in heart homogenates *in vitro*<sup>15</sup>—was used as a potent free radical scavenger in Friedreich's ataxia.<sup>16</sup>

We used an antioxidant rather than an iron chelator such as desferrioxamine (deferrioxamine) for several reasons. Firstly, the decrease in cytosolic iron associated with mitochondrial iron overload in Friedreich's ataxia may play a role in the pathogenesis of the disease, making a further reduction in cytosolic iron by desferrioxamine possibly detrimental.<sup>8,9</sup> We have previously shown that desferrioxamine does not act as an antioxidant, but rather displaces iron from biological membranes to the soluble phase (thus protecting them), and so triggers the destruction of soluble enzymes, such as aconitase, that are already targeted in Friedreich's ataxia.<sup>16</sup> Moreover, it has been shown that desferrioxamine fails to improve the impairment in postschaemic cardiac function caused by free radical overproduction in hypertrophic rabbit hearts.<sup>21</sup> Finally, no evidence of increased circulating iron has been found,<sup>22</sup> and we have occasionally even observed low circulating iron in patients with Friedreich's ataxia (unpublished data). For all these reasons, the use of an iron chelator did not seem logical.

We selected idebenone from among various different antioxidants for several reasons. Firstly, most antioxidants, including vitamin C but not idebenone,<sup>16</sup> readily reduce iron, and this has been shown to be detrimental in cases of disturbed iron homeostasis.<sup>23</sup> Also, compared with the highly hydrophobic antioxidants capable of scavenging lipoperoxyl radicals (such as vitamin E), idebenone directly reduces the superoxide radicals involved in the early steps of iron induced damage. Finally, we considered idebenone—which is taken up by cells and crosses the blood–brain barrier<sup>16</sup>—to be preferable to CoQ<sub>10</sub>, which is only taken up by cells lacking the natural quinone.<sup>24</sup>

In this paper, we show that six months of oral idebenone treatment resulted in a significant decrease (by more than 20%) in cardiac hypertrophy in half the patients with Friedreich's ataxia. Because spontaneous recovery has never been reported, we believe that the present study supports preliminary data showing the efficacy of idebenone in controlling cardiac hypertrophy in Friedreich's ataxia.<sup>16</sup> Idebenone has recently also been shown to reduce the oxidatively modified DNA that is found in the urine of patients with Friedreich's ataxia.<sup>25</sup>

No correlation between drug efficacy and age, sex, initial severity of cardiac hypertrophy, or size of the triplet expansion in the frataxin gene could be found. Variation in the efficacy of the drug among affected individuals thus remains unexplained. However, the dose of the drug required for a therapeutic effect is likely to vary between individuals, as increasing the dose to 10 mg/kg/day had a dramatic effect in one patient

who had failed to respond to the initial dose of 5 mg/kg/day. Because of its absence of side effects, an increased idebenone dose should be considered in patients who fail to respond to the initial dose.

It should be remembered that the pathogenesis and the natural course of cardiomyopathy in Friedreich's ataxia remain largely unexplained.<sup>26</sup> In particular, the occurrence of a hypokinetic dilated cardiomyopathy is not rare,<sup>26-28</sup> possibly representing a complication in patients who originally had a hypertrophic left ventricle.<sup>3</sup> It is tempting to hypothesise, therefore, that responsiveness to the drug is related to the kinetic properties of the affected myocardium. In this regard, the improved cardiac contractility and shortening fraction observed after an increased dose of idebenone in one of our patients indicates that improvements in ventricular systolic function can occur with idebenone even though the left ventricular mass has been reduced. Thus idebenone does not interfere with myocardial adaptive hypertrophic processes aimed at preserving left ventricular function.

### Conclusions

These data indicate that none of the variables tested could predict the efficacy of idebenone in treating patients with Friedreich's ataxia. This suggests that idebenone is worth trying in such patients irrespective of the size of the GAA expansion and the initial ultrasound findings. In the future, a combination of more hydrophobic antioxidants, such as vitamin E,<sup>29</sup> with idebenone should also be investigated in these patients. Finally, idebenone trials currently being undertaken in frataxin knockout mice may answer the question as to whether idebenone can prevent the onset of cardiomyopathy and neurological involvement in Friedreich's ataxia.

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