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Antioxidant use in Friedreich ataxia

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Summary

Many antioxidants have been suggested as potential treatments for Friedreich ataxia, but have not been tested in clinical trials. We found that a majority of patients in our cohort already use such antioxidants, including idebenone, which is not available at a pharmaceutical grade in the United States. Younger age, cardiomyopathy and shorter GAA repeat length were independent predictors of idebenone use, but no factors predicted use of other antioxidants. This confirms that non-prescription antioxidant use represents a major confounder to formal trials of existing and novel agents for Friedreich ataxia.

Keywords

ataxia; idebenone; clinical trial; cerebellum

Friedreich ataxia (FA) is an autosomal recessive disorder characterized by progressive ataxia, dysarthria, diabetes, scoliosis and cardiomyopathy (1). An expanded GAA triplet repeat is found in both alleles of the *FRDA* gene in 97% of people with FA (1,2). The length of the shorter GAA repeat correlates with age of onset. Frataxin, the gene product of *FRDA*, chaperones iron in the mitochondrial matrix, and may be involved in the assembly and repair of mitochondrial iron-sulfur clusters (3–5). Loss of mitochondrial respiratory function and the production of reactive oxygen species are postulated to contribute to the disease. While some

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antioxidants improve biomarkers of disease activity (6,7), double blind clinical trials are necessary to determine the effect of antioxidants on clinical measures in FA.

Since many antioxidants are available without a prescription, some patients use antioxidants in an attempt to slow disease progression. We reviewed the data available from a large multicenter study of FA to ascertain the prevalence of antioxidant use in FA and the disease features associated with use of antioxidants. This information about medication and supplement use in the FA population will be important in planning future clinical trials.

Methods

We examined 217 patients with genetically confirmed FA at 7 sites: The University of Pennsylvania/Children's Hospital of Philadelphia (67); University of California, Los Angeles (73); Emory University (33); University of Mississippi Medical Center (16); University of Minnesota (17); University of Iowa (8); and the University of Texas Medical Branch (3). Patients were assessed with a quantitative neurological exam called the Friedreich Ataxia Rating Scale (FARS) (8). Use of the antioxidants vitamin E, idebenone, coenzyme Q10, selenium, N-acetyl cysteine (NAC) and other medications were recorded, as well as the dosage and duration of therapy. Dosages were also converted to dose per weight when possible.

Data analysis

Logistic regression analyses were used to define contributors to the use of antioxidants. Analyses were performed using Stata 8.0 software (StataCorp, College Station, TX). Statistical significance was set at $p < 0.01$ since multiple comparisons were performed.

Results

The cohort had a mean age of 30.8 ± 15.5 years, and 57% were women. Mean shorter GAA repeat length was 602 ± 247 . Forty one percent of subjects had cardiomyopathy, 76% had scoliosis, and 5% had diabetes. Mean FARS score was 66 ± 23 , typical of a barely ambulatory patient.

Use of antioxidants was common among this cohort. Only 36% of patients reported no antioxidant use, and 1% took all five antioxidants queried (Table 1). Vitamin E was the most commonly taken antioxidant, followed by coenzyme Q10. Side effects were quite limited and included easy bruising with vitamin E (1 patient), increased cholesterol levels after starting CoQ10 in conjunction with cholesterol lowering medicines (1 patient), and nausea with combination NAC/selenium (1 patient). For comparison, symptomatic prescription medications taken by patients included baclofen (11%), buspirone (3%), gabapentin (6%) and amantidine (6%), showing that antioxidant use was far more prevalent than prescription medication use.

We then examined whether antioxidant use was associated with specific clinical features of FA patients. Antioxidant use did not differ between sites (data not shown). Idebenone use was independently associated with younger age and shorter GAA repeat size; presence of cardiomyopathy was also independently associated with a higher probability of taking idebenone with an odds ratio of 3.3 (though this did not reach significance ($p > 0.01$)). In addition, the median dose of idebenone (about 7 mg/kg) is similar to that suggested to slow the progression of cardiomyopathy (7). When we reviewed the cumulative data, 38% of children already took idebenone, and 72% of children took at least one antioxidant. Better neurological exam score showed a trend toward increased use of each antioxidant except NAC; this did not reach significance, suggesting that disease stage did not greatly influence tendency

toward such therapies. No other features were significantly associated with an increased use of any other specific antioxidant.

Discussion

In the present study we determined that a majority of FA patients use readily available antioxidants. Except for use of idebenone, there were no predictors for use of other specific antioxidants in terms of genetic severity, gender, or age. While these agents are not clearly efficacious and may theoretically counteract each other in certain situations (11), the level of antioxidant use seems quite high in comparison to other neurodegenerative disorders. This may reflect the publication of studies almost 10 years ago suggesting potential efficacy of idebenone, the life threatening nature of cardiomyopathy in FA, the relative justification in intervening in a childhood-onset (rather than adult-onset) disorder, and the biased nature of the referral population in the present study. In the primary center in the present study (University of Pennsylvania/CHOP), almost 50% of patients live outside normal referral areas suggesting the possibility of bias. Still, in each of the centers, less than 10% of patients seen for FA declined participation, limiting further bias (data not shown). In addition, this referral population is likely the target of future therapeutic trials, making the present observations directly relevant for such studies.

The use of non-prescription medicines and alternative therapies has been associated with a variety of factors in other settings (12–15). Gender, racial and ethnic features, and disease severity have all been associated with alternative medical approaches in selected populations. In our cohort, ethnic and racial features play little or no role because of the limited racial distribution of FA, and we found no influence of gender as a determining factor in antioxidant use. Disease severity (as defined by FARS score) also played at most a limited role. In contrast, use of idebenone was associated with younger age, shorter GAA repeat length and cardiomyopathy. Several studies suggest that idebenone may be efficacious in young patients with cardiomyopathy, and the dose used here by FA patients roughly matches that used in European trials (7,9,10), suggesting that the use of idebenone in part reflects reading of the medical literature by physicians and families. The association of idebenone use with shorter GAA repeat length when age is controlled likely reflects the subpopulation of adults with late onset disease that are more readily capable of obtaining idebenone. In the present cohort, antioxidant use was usually initiated by patients, though physicians were generally consulted. This is revealed in our data by the absence of any site dependence in antioxidant use.

The present data illustrate the need for systematic clinical trials when feasible, but also have important implications for the design of clinical trials in FA, particularly if the agent under consideration has antioxidant properties. Most proposed trials in FA will use a placebo control and require discontinuation of antioxidants in order to maximize detection of a response to therapeutic agents (most of which have some antioxidant abilities). As initial clinical trials may be targeted to children who are ambulatory (based on the presumed superior responsiveness of such patients), our data demonstrate that most children are at present not eligible for such trials unless they discontinue present agents. However, the widespread use of antioxidants suggests that patients and caregivers already believe that such agents are useful. Thus it may be difficult to find patients who are antioxidant naive or willing to discontinue antioxidant use for clinical trials. This dramatically limits the enrollment possibilities and the generalizability of results from such studies.

In considering the design of future trials, it may be necessary to minimize the number of individuals in placebo arms or to limit the time of such trials to avoid long-term withholding of such agents. Alternatively, careful natural history studies might allow use of historical controls using antioxidants in some trials, or studies could utilize an active placebo arm

containing low dose antioxidants. Some trials might allow for continued intake of current antioxidants with stable dosing. Accurate knowledge about the current health practices of potential study participants will allow study design to optimize enrollment and insure meaningful results.

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Table 1

Table 1A. Use of Antioxidants in FA patients

Table 1B. Logistic regression analysis of clinical variables and antioxidant use

Agent	% taking	Median dose	Interquartile Range	Median Dose/weight	Interquartile Range	Median Duration (years)
Vitamin E	53	800 IU	700–1200	11.3 IU/kg	8.2–20 IU/kg	>1
Coenzyme Q10	43	300 mg	200–400	3.9 mg/kg	2.2–7.7 mg/kg	>1
Idebenone	17	390 mg	225–450	6.8 mg/kg	4.4–10 mg/kg	>1
NAC	9	1100 mg	550–2250	29.5 mg/kg	15.8–52.4 mg/kg	>1
Selenium	7	200 mg	100–200	2.7 mg/kg	0.98–4.7 mg/kg	>1
Agent	Age	Gender	GAA Repeat Length	Presence of Cardiomyopathy	FARS score	
Vitamin E	0.56	0.37	0.59	0.32	0.052	
CoQ	0.73	0.69	0.35	0.50	0.13	
Idebenone	0.0005*	0.32	0.005*	0.029	0.13	
NAC	0.24	0.41	0.073	0.97	0.54	
Selenium	0.32	0.54	0.14	0.62	0.025	

* =statistically significant. In panel A, the use of different antioxidants is displayed. In panel B, Logistic regression was used to define the patient characteristics associated with a greater likelihood for use of each antioxidant (*p* values shown in table).