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Friedreich Ataxia Clinical Outcome Measures: Natural History Evaluation in 410 Participants

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Abstract

Friedreich ataxia is an autosomal recessive neurodegenerative disorder characterized by ataxia, dysarthria, and areflexia. We report the progress of a large international non-interventional cohort (n = 410), tracking the natural history of disease progression using the neurological exam-based Friedreich Ataxia Rating Scale. We analyzed the rate of progression with cross-sectional analysis and longitudinal analysis over a 2-year period. The Friedreich Ataxia Rating Scale captured disease progression when used at 1 and 2 years following initial evaluation, with a lower ratio of standard deviation of change to mean change over 2 years of evaluation. However, modeling of

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disease progression identified substantial ceiling effects in the Friedreich Ataxia Rating Scale, suggesting this measure is most useful in patients before maximal deficit is approached.

Keywords

clinical neurology; Friedreich ataxia; natural history study; non-interventional study

Introduction

Friedreich ataxia is an autosomal recessive disorder caused by mutations in the gene *FXN*.¹ Ninety-seven percent of people with the disorder have an expanded GAA triplet repeat in both alleles, whereas the remaining 3% of patients carry an expanded GAA repeat on one allele and a point mutation on the other.² The length of the shorter GAA repeat correlates with age of onset ($r = 0.6-0.7$).^{3,4} The repeat is in the first intron, and its expansion leads to decreased messenger RNA transcription and a deficiency of the protein frataxin.¹ Similarly, point mutations in *FXN* lead to absence of functional frataxin.^{2,5}

Neurological manifestations of Friedreich ataxia are progressive and include ataxia, loss of coordination, dysarthria, and extensor plantar responses. Patients can also have scoliosis, cardiomyopathy, diabetes, pes cavus, bladder dysfunction, optic atrophy, and hypoacusis.⁶⁻⁸ Onset typically occurs in late childhood or early adolescence, but can be as late as the seventh decade of life.⁹⁻¹¹ At present, there is no approved treatment in the United States, although several clinical trials have been conducted in the past 5 years.¹²⁻¹⁶

Investigational drug trials in Friedreich ataxia have been aided by the presence of several ongoing natural history studies that have assessed the rate of change in Friedreich ataxia with quantifiable measures.^{17,18} Measures used for quantitation of neurological function include the neurologic exam-based Friedreich Ataxia Rating Scale,¹⁷ which has been used as an outcome measure in several clinical trials.^{12,19,20} As previously shown in modest-sized cross-sectional analysis and in longitudinal analysis after 2 years of follow-up, the scale captures disease progression in Friedreich ataxia.^{4,9} This study provides interim analysis of the average rates of change over 2 years in an expanded cohort of patients with Friedreich ataxia from the American/Australian natural history study, using the Friedreich Ataxia Rating Scale examination.

Methods

This study had the approval of each site's Institutional Review Board, and participants provided written informed consent before enrolling. The cross-sectional cohort of individuals ($n = 410$) with genetically confirmed Friedreich ataxia was examined at one of 9 institutions: Children's Hospital of Philadelphia and the University of Pennsylvania (156 participants), University of California Los Angeles (95 participants), Murdoch Children's Research Institute (66 participants), Emory University (52 participants), University of Minnesota (18 participants), University of Iowa (11 participants), University of Chicago (8 participants), and University of Rochester (4 participants). All participants with a follow-up visit at year 1 or 2 from baseline were included in longitudinal analysis. This is an actively enrolling study and some participants were not yet in window for year 1 or 2 visits. For transition analysis, visits beyond the first 2 years (out through year 6) were also used. Interim reports on smaller versions of this cohort have appeared previously.^{4,9}

Longitudinal analysis was performed on 251 participants who returned for their 1 year after baseline (V01) or 2 years after baseline (V02) examinations. Of those who returned, we

calculated the change from baseline to year 1 and year 2, as well as the yearly rate of change in the Friedreich Ataxia Rating Scale,^{4,9} performed as described previously. Data analysis was performed using Stata 11.2 software (Stata-Corp, College Station, Texas) using regression models, correlations, transition charts, and analysis of variance (ANOVA). Clinical and demographic information were obtained at the baseline visits and included age of symptom onset, length of GAA repeats, age at exam, and sex.

In some analysis the population was stratified to examine progression rates for subpopulations. Subpopulations were created by stratifying for length of the shorter GAA repeat (<300, >300–600, >600), sex, age (<18 or ≥18), and Friedreich Ataxia Rating Scale score (<70 or ≥70).

To analyze ceiling and floor effects, annual changes in Friedreich Ataxia Rating Scale score were assessed at different Friedreich Ataxia Rating Scale ranges. Each exam was categorized into a particular range and analyzed chronologically for transitions between ranges. Friedreich Ataxia Rating Scale ranges were set equal to 10 points, giving a total of 12 divisions (with the top division ending at the maximum Friedreich Ataxia Rating Scale score of 117). The 10-point range was selected after reviewing progression rates from previous manuscripts. If the yearly Friedreich Ataxia Rating Scale change resulted in a transition to a higher Friedreich Ataxia Rating Scale range, the change was recorded as an increase. The transition probability for each range was then calculated as the number of individuals progressing to the next range divided by the number of individuals originally in the range. A minority of patients (6%) made Friedreich Ataxia Rating Scale transitions between non-adjacent Friedreich Ataxia Rating Scale ranges; these were excluded from the initial analysis. If patients had Friedreich Ataxia Rating Scale scores in the decimal range between 2 ranges, then all scores greater than 0.5 were rounded up to the higher range. To account for the effect of reverse transitions, the transition probabilities for reverse Friedreich Ataxia Rating Scale transitions were calculated as the negative of the number of reverse transitions divided by number of individuals in the original range. This ensured that the reverse directionality of the transition was accounted for. A weighted average of the forward and reverse transitions was taken. This analysis was performed for all patients, as well as for individuals within each GAA repeat length subpopulation.

Results

Cohort Features

From our cross-sectional cohort of 410 participants with Friedreich ataxia, 259 (63%) returned for follow-up visits over the next 6 years after baseline. When we adjusted for the fact that some participants who enrolled later in the study were not yet within the time frame for V01 when data analysis occurred, the return rate was (79%) overall at 1 to 6 years, with return rates of 69% at V01 and 64% at V02. The average length of GAA repeats in the shorter allele was 662 ± 247 . There were 15 patients with point mutations (1 A460T, 1 G130V, 1 I154F, 1 L106S, 1 L182F, 1 W154R, 1 R165C, 1 Del A+3 Intron 4, 1 splice site mutation, 6 unidentified). The average age of onset for the cohort was 13.7 years. The cross-sectional cohort had an average Functional Disability Score⁴ of 3.5 and a Friedreich Ataxia Rating Scale score of 63.7, which is equivalent to a person walking with moderate to severe ataxia. To ensure there was no selection bias in the patients who returned for follow-up, we compared the clinical and demographic features of the cross-sectional and longitudinal cohorts at each year. The groups were similar in sex, age of onset, and testing site (data not shown). The longitudinal cohort was predominantly adult (69.4%).

Cross-sectional Analysis of Friedreich Ataxia Rating Scale Scores

To analyze factors influencing Friedreich Ataxia Rating Scale exam scores, we initially performed cross-sectional analysis over the entire cohort using multivariate regression. Scores were predicted by age and length of the shorter GAA repeat, while sex and exam site did not predict scores (Table 1). When displayed graphically as function of duration, there was a clear difference among participants with different GAA repeat lengths (Figure 1). There was substantial variability with Friedreich Ataxia Rating Scale score as a function of duration in patients with GAA repeats of 300 or less ($r = 0.56$). In individuals with intermediate-length repeats (300 to 600), the Friedreich Ataxia Rating Scale score generally was linear with duration ($r = 0.81$). However, in participants with long GAA repeats, the relationship became nonlinear at longer durations ($r = 0.70$), suggesting that participants reach the ceiling of the scale (Figure 1).

Longitudinal Analysis

We then analyzed the observed progression rates over 2 years. The Friedreich Ataxia Rating Scale captured disease progression as demonstrated by scores at year 1 and 2 that were significantly different than baseline, with a substantially better ratio of standard deviation of change to mean change at year 2 compared with year 1 (Table 2). Still, the ratio was relatively high for use in a nonstratified clinical trial; consequently, we examined rates of change in subpopulations. Children progressed over twice as fast as measured by the Friedreich Ataxia Rating Scale over 1 year (Table 3). Progression was perhaps slightly faster in female participants (Table 3). We also stratified results by GAA repeat length. For participants with GAA repeat lengths less than 300, the Friedreich Ataxia Rating Scale change was only moderately significant within the 2-year period, reflecting not a lack of change but a high variability in the rate of change. Progression rates for the intermediate and long GAA repeat groups were faster, with greater ratios of standard deviation of change to mean change. In addition, change was slower in participants with Friedreich Ataxia Rating Scale scores greater than 70.

To further explore the apparent ceiling effects of the Friedreich Ataxia Rating Scale, transition probability analysis was performed. Based on transition analysis, the relative amount of Friedreich Ataxia Rating Scale score change decreased as score increased (Figure 2). For the entire cohort the transition probability decreased from 0.4 at a baseline Friedreich Ataxia Rating Scale score of 30 to 39 to a negative transition at a baseline of 100 to 109. Interestingly this fall was relatively steep; the transition probability fell only slightly between baseline scores of 30 to 39 and 70 to 79, but fell rapidly with each subsequent transition group. However, when groups were stratified by GAA repeat length, the fall in transition probability seen between a baseline score of 30 to 39 and 50 to 59 was more obvious, as the subpopulation with the shortest GAA repeat length behaved differently. This group changed more slowly at low scores than the patients with longer GAA repeats and never reached the ceiling of the scale. Overall, the differences based on GAA repeat length were modest.

However, in the transition probability analysis, we could not include the small number of transitions greater than one Friedreich Ataxia Rating Scale range. Since these subjectively appeared to occur more frequently in individuals with lower baseline scores, this exclusion might obscure floor effects. Consequently, we also looked at the mean change in score within each transition group (Figure 3). Overall, the yearly change in score was relatively constant between baseline scores of 30 and 89, but then fell after that point. This confirms the presence of a significant ceiling effect on the Friedreich Ataxia Rating Scale, but a relatively consistent yearly change at scores below 89.

Discussion

In this study we analyzed Friedreich Ataxia Rating Scale scores in a large heterogeneous cohort with cross-sectional analysis and longitudinal analysis of change over 2 years in a natural history study. As noted in our previous studies of a smaller group within this cohort, the ratio of standard deviation of change to mean change is much lower after 2 years of evaluation, suggesting that for unselected cohorts, 2 years may be the minimum needed for reasonable power in clinical trials. However, the data from stratifications show that younger participants or those with longer GAA repeat lengths change substantially faster than the overall cohort. This suggests that the population segments with these characteristics may be the best targets statistically for such trials. Patients with short GAA repeats changed somewhat slower, but more impressively, this group showed a highly variable progression rate both when examined cross sectionally and longitudinally. This variability may be useful in modifier gene analysis to allow assessment of non-*FXN*-mediated genetic variability in Friedreich ataxia.

The cross-sectional analysis and transition analysis both identified a substantial ceiling effect in the Friedreich Ataxia Rating Scale. The transition probability and the apparent rate of change slowed with scores greater than 89, but were relatively constant to that point. Conceptually, all scales with fixed endpoints (117 for the Friedreich Ataxia Rating Scale exam) must have ceiling effects (though they may not be apparent in a given cohort).¹⁸ The ability to statistically identify such ceilings depends on the size and composition of the cohort. However, the transition probability analysis defines the range in which ceiling effects begin to occur. Interestingly, in the participants with longest GAA repeats, an apparent ceiling appeared with time, which was not as apparent with participants with shorter repeat lengths. This emphasizes the more rapid change that occurs before they reach the ceiling of the Friedreich Ataxia Rating Scale. As noted before in the smaller version of this cohort, women appear to progress at a slightly faster rate. The reason for this is still unclear but has been noted in other cohorts.²¹ Overall, the present work emphasizes the validity of this instrument as well as its limitations, and provides a framework for its use in future investigations.

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Figure 1. Change in FARS score with disease duration

Friedreich Ataxia Rating Scale shown as function of disease duration in the subpopulations based on GAA repeat length >600 (A), >300 – 600 (B), and 300 (C).

Figure 2. Friedreich Ataxia Rating Scale score transition probabilities

Friedreich Ataxia Rating Scale score transition probabilities are shown as function of Friedreich Ataxia Rating Scale range. All observations are shown in panel (A), and are stratified by GAA repeat length in panel (B).

Figure 3. Average Friedreich Ataxia Rating Scale change in each FARS range

The average Friedreich Ataxia Rating Scale change for participants at different Friedreich Ataxia Rating Scale ranges is shown for all observations in panel (A) and stratified by GAA repeat length in panel (B).

Table 1

Cross-sectional Analysis of FARS Scores

Measure	GAA	Coeff.	Sex	Coeff.	Age	Coeff.	Overall	Overall R ²
FARS	>0.001	.0484	0.496	-1.30	>0.001	.797	>0.001	0.356

Linear Regression was used to examine the effect of GAA repeat length, age, and sex on baseline FARS scores. Significance values for each variable are listed under GAA, Sex, and Age. Site was included as a dummy variable and did not predict FARS (data not shown). The total number of participants with complete information was 353.

Abbreviations: Coeff, Regression coefficient; FARS, Friedreich Ataxia Rating Scale; Sig, significance.

Table 2

Change in FARS Exam Stratified by Year to Baseline

FARS	Baseline To Year 1			Baseline To Year 2			All Observations		
	Sig.	Mean ± SD (FARS U/year)	N	Sig.	Mean ± SD (FARS U/year)	N	Sig.	Mean ± SD (FARS U/year)	N
	0.000	2.66 ± 7.14	249	0.000	6.20 ± 10.7	249	0.000	2.89 ± 4.27	251

The yearly change in FARS scores were determined by Regression analysis for change from baseline to year 1; change from baseline to year 2; and using all observations.
Abbreviations: FARS, Friedreich Ataxia Rating Scale; Sig, significance; SD, standard deviation

Table 3

Analysis of Change in FARS Scores by Subpopulations

Stratification	Adult			Pediatric		
	Sig.	Mean $\pm$ SD (FARS U/year)	N	Sig.	Mean $\pm$ SD (FARS U/year)	N
Age						
	<0.001	2.02 $\pm$ 4.02	176	<0.001	4.71 $\pm$ 5.46	91
	GAA	300		GAA > 300 and 600		
GAA						
	Sig.	Mean $\pm$ SD (FARS U/year)	N	Sig.	Mean $\pm$ SD (FARS U/year)	N
	0.038	1.58 $\pm$ 4.14	24	<0.001	2.63 $\pm$ 3.58	79
	Male			Female		
Sex						
	Sig.	Mean $\pm$ SD (FARS U/year)	N	Sig.	Mean $\pm$ SD (FARS U/year)	N
	<0.001	3.09 $\pm$ 4.27	129	<0.001	2.70 $\pm$ 4.27	122
	FARS	70		FARS < 70		
FARS Score						
	Sig.	Mean $\pm$ SD (FARS U/year)	N	Sig.	Mean $\pm$ SD (FARS U/year)	N
	<0.001	2.88 $\pm$ 4.72	158	<0.001	1.76 $\pm$ 4.19	117