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Measuring the rate of progression in Friedreich ataxia: Implications for clinical trial design

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Abstract

Friedreich ataxia is an autosomal recessive neurodegenerative disorder characterized by ataxia of all four limbs, dysarthria and areflexia. A variety of measures are currently used to quantify disease progression, including the Friedreich Ataxia Rating Scale, examiner-rated functional disability scales, self-reported activities of daily living and performance measures such as the timed 25-foot walk, 9-hole pegboard test, PATA speech test, and low-contrast letter acuity vision charts. The present study examines the rate of disease progression over one and two years in a cohort of 236 Friedreich ataxia patients using these scales and performance measure composites. The Friedreich Ataxia Rating Scale and performance-measure composites captured disease progression, with a greater sensitivity to change over two years than over one year. The measures differed in their sensitivity to change and in possible bias. These results help to establish norms for progression in FRDA that can be useful in measuring the long-term success of therapeutic agents and defining sample-size calculations for double-blind clinical trials.

Keywords

ataxia; natural history study; clinical neurology examination; mitochondrial disorder; trinucleotide repeat disease

Introduction

Friedreich ataxia (FRDA), the most common inherited ataxia with a prevalence of 1 in 50,000, is an autosomal recessive disorder [1] caused by mutations in the gene *FXN* [2]. 97% of people with the disorder have an expanded GAA triplet repeat in both alleles [3]. This repeat in the first intron leads to decreased mRNA transcription and a deficiency of the protein frataxin. The length of the shorter GAA repeat correlates with age of onset ($r=0.6-7$) [4]. The remaining 3% of patients carry an expanded GAA repeat on one allele, and a point mutation on the other allele [5–7].

Clinical manifestations of FRDA include ataxia, loss of coordination and reflexes, dysarthria and extensor plantar responses [8–10]. Patients can also have scoliosis, pes cavus, diabetes, incontinence, cardiomyopathy, optic atrophy and hypoacusis [1,10,11]. Typical onset occurs in late childhood or early adolescence, but is variable [9]. At present, there is no approved treatment in the US, although the antioxidant Idebenone is in a phase III clinical trial [12].

Because clinical trials require valid methods to quantify how patients change over time, attention has focused on the development of effective disease rating scales. One is the Friedreich Ataxia Rating Scale (FARS), a clinical examination-based measure with good inter-rater reliability [13]. The FARS has five separate subscores and has been used in clinical trials [14]. In addition to the FARS, performance measures analogous to those used in the Multiple Sclerosis Functional Composite have been modified for use in FRDA patients [13]. These performance measures include a 9-hole peg test (9HPT) for arm function, a timed 25-foot walk (T25FW) for ambulation, a speech test using the phrase “PATA,” and a low-contrast letter acuity vision test (LCLA).

Currently, there are few norms for predicting rates of change for FRDA patients across any of the measures. This study examines the average rates of change over one and two years in a large cohort of FRDA patients in the FARS, performance measures, self-reported Activities of Daily Living (ADL), and an examiner-measured Functional Disability Scale (FDS). We also assessed the rates of change in two z-score composites: Z2 defined by adding the z scores of the reciprocal of the 9-hole peg test ($9HPT^{-1}$) and the reciprocal of the timed 25 foot walk ($T25FW^{-1}$), and Z3, defined by adding the z scores of $9HPT^{-1}$, $T25FW^{-1}$ and LCLA. Additionally, we assessed the rate of change in the Expanded FARS (E-FARS), defined by adding the FARS, ADL and FDS scores together [15]. These results help to establish norms for progression in FRDA that can be useful in measuring the long-term success of therapeutic agents and defining sample-size calculations for double-blind clinical trials.

Methods

This study had the approval of all Institutional Review Boards. All subjects provided written informed consent before participating in study procedures.

We examined 236 patients (FRDA cross-sectional cohort) with genetically confirmed FRDA at the University of Pennsylvania/Children's Hospital of Philadelphia (82 patients), University of California, Los Angeles (75 patients), Emory University (32 patients), University of Mississippi (19 patients), University of Minnesota (18 patients), University of Iowa (9 patients) and the University of Texas Medical Branch (1 patient).

From the cross-sectional cohort, 168 patients (FRDA longitudinal cohort) returned for at least one follow-up. Of those who returned, we calculated rate of change from baseline to year one or two in the 9HPT, T25FW, PATA, LCLA, ADL, FDS, FARS, E-FARS, Z2 and Z3. Tests were performed as described previously [13].

For the 9HPT, the mean of the scores from two trials with each hand was calculated independently. Then the reciprocal of the mean ($9HPT^{-1}$) was calculated and the rate of change was found by subtracting $9HPT^{-1}$ baseline from $9HPT^{-1}$ year 1 or year 2. Negative scores indicated disease progression. When a patient failed to complete the 9HPT, we determined if this was disease related. 27 patients failed to complete the 9HPT at one or more visits; in 23 this was related to FRDA. For analyses, patients unable to complete tests due to FRDA-related factors were given a score of infinity (thus a $9HPT^{-1}$ score of zero), while patients unable to complete the test for unrelated reasons were excluded from analyses.

For the T25FW, the mean of two trials was the summary measure. The reciprocal of the mean ($T25FW^{-1}$) was calculated. Rate of change was calculated as described for the 9HPT. Negative scores indicated disease progression. 93 patients failed to complete the T25FW at least once; in 90 this was related to FRDA.

For PATA, the mean of two trials was the summary measure. Rate of change was calculated by subtracting $PATA_{baseline}$ from $PATA_{year 1 \text{ or } year 2}$. Negative scores indicated disease progression. Six patients failed to complete the PATA at least once; in one this was related to FRDA.

For LCLA, the summary measure was the number of correct letters read using both eyes for three charts: 100% contrast from a distance of 3.2 meters, and 1.25% and 2.5% contrast from a distance of 2 meters [13]. Each chart had a maximum score of 70 letters, with an overall total of 210 letters. Rates of change were calculated by subtracting $LCLA_{year 1 \text{ or } year 2}$ from $LCLA_{baseline}$. Positive scores indicated disease progression. 10 patients failed to complete the LCLA at least once; in three this was related to FRDA.

ADL is scored from 0 to 36, with higher scores representing more severe progression. For ADL, rates of change were calculated by subtracting $ADL_{\text{year 1 or year 2}}$ from ADL_{baseline} . Positive scores indicated disease progression. 23 patients failed to complete the ADL at least once due to time constraints. These visits were excluded from analyses.

FDS is scored from 0 to 6 with higher scores representing more severe progression. Rates of change for the FDS were calculated by subtracting FDS_{baseline} from $FDS_{\text{year 1 or year 2}}$. Positive scores indicated disease progression. 7 patients did not receive a FDS at least once; these were excluded from analyses.

The FARS is scored from 0 to 125 with higher scores representing more severe progression. Rates of change were calculated by subtracting $FARS_{\text{baseline}}$ from $FARS_{\text{year 1 or year 2}}$. Positive scores indicated disease progression. 14 patients failed to complete the FARS at least once; these visits were excluded from analyses as none were related to disease progression. We also analyzed the rate of change for each subscore on the FARS exam: the bulbar portion, upper and lower extremities, peripheral portion and upright stability. For each subscore, we followed the formula of subtracting $FARS_{\text{subscore baseline}}$ from $FARS_{\text{subscore year 1 or year 2}}$. A negative score indicated improvement.

The E-FARS is scored from 0 to 167, with higher scores representing more severe progression. The E-FARS was calculated by adding the FARS, ADL and FDS scores [14]. Rates of change were calculated by subtracting $E\text{-FARS}_{\text{baseline}}$ from $E\text{-FARS}_{\text{year 1 or year 2}}$. Positive scores indicated disease progression.

Composite z scores from the $9HPT^{-1}$ and $T25FW^{-1}$, designated Z2, and $9HPT^{-1}$, $T25FW^{-1}$ and LCLA, designated Z3, were calculated [13]. To create a z score for a test, we subtracted the cohort mean for each measure from the raw score and divided it by the cohort standard deviation for that measure. For Z3, we added the z scores of $9HPT^{-1}$ and $T25FW^{-1}$ and subtracted the z scores of LCLA. Negative changes in Z2 and Z3 indicated disease progression.

Cohort means and standard deviations used in the calculations were as follows: $9HPT^{-1}$: 0.015 ± 0.010 , $T25FW^{-1}$: 0.065 ± 0.082 , LCLA: 108.63 ± 38.10 , PATA: 14.73 ± 6.32 , FDS: 3.95 ± 1.35 , ADL: 15.21 ± 8.18 , FARS: 67.88 ± 25.86 .

Data analyses (correlation coefficients, linear regression) were performed using Stata 10.0 software (StataCorp, College Station, TX) as described previously [13]. Hypothetical sample size calculations for different measures were made for a theoretical 2 arm interventional study using the mean changes in measures presuming a 50% slowing of disease progression with an equal improvement in standard deviation..

Results

From our cohort of 236 patients, 159 subjects (67.4%) returned for a one-year follow-up visit approximately nine to fifteen months after baseline. Some patients who enrolled later in the study were not yet within the time frame for a two-year visit when data analysis occurred. 124 patients (71.3% of 174 eligible subjects) returned for a two-year follow up visit, approximately 21 to 27 months after baseline.

To ensure there was no selection bias in the patients who returned for follow-up, we compared the clinical and demographic features of the longitudinal and cross-sectional cohorts. The two groups were similar in sex, age, FARS score, age of disease onset, length of shorter GAA repeat and testing site (data not shown). Both the longitudinal and cross-sectional cohort contained nearly four times as many adults as children ($79.3\% \geq \text{age } 18$).

We then examined the rates of change of the performance measures (Table 1). All of the measures except for the PATA test were distributed normally and thus the data was analyzed using parametric statistics. By inspection, the $9HPT^{-1}$ changed appeared linear over time, as shown by a proportional change in means between baseline and year one and two. The $T25W^{-1}$, LCLA and PATA did not, suggesting that scores from asymptomatic and maximally affected patients may be altered by floor or ceiling effects. PATA test scores showed no change over time, and thus this test was not a meaningful measure of disease progression.

To evaluate change in composite performance measures, we calculated the Z2 and Z3 composite measures (Table 1). The PATA test was excluded from the composites because of its previously described weak correlation with disease features and its failure to measure disease changes [13]. By inspection, both Z2 and Z3 mean values appeared to change linearly over the two-year study. We also evaluated the ratio of standard deviation of change to mean change (SD/mean). In clinical trials, the sample size depends directly on this ratio, with larger ratios demonstrating the need for a larger sample size. The SD/mean ratio was substantially lower for a two-year period than a one-year period for all performance measures except PATA.

We then evaluated the FARS, FDS, ADL and E-FARS (Table 1). The distribution of change in means in the FARS and FDS was not skewed, and both declined significantly over time. For both, the change in the second year was somewhat less than in the first year. The E-FARS also had a mean change that was not proportional between one and two years of follow-up. In contrast, the ADL scale had a more proportional change in means between the first and second years, and also was not skewed. The neurologic exam and disability-based measures also had lower ratios of SD/mean over a two-year time period.

While all of the measures had better ratios of standard deviation of change to change at two years than one year, the expected sample sizes for simple clinical trials remain substantial. For a one year trial comparing mean change in scores with an expected slowing of disease progression by 50%, the E-FARS would require 133 patients per arm, with the other measures requiring substantially more. At two years, the numbers are substantially lower for the Z3 (100 patients per arm), FARS (75 per arm), and E-FARS (52 per arm).

We also assessed the five subscores of the FARS to determine if any individual component had a larger effect on total change (Table 2). The smallest change was seen in the peripheral and bulbar scores, while upper, lower and upright stability scores changed more substantially, suggesting that these subscores drive the change in FARS over time. The five also had relatively low correlations with each other, suggesting that each subscore measures a unique dimension of FRDA (data not shown).

Stratified analysis and linear regression

We then assessed the effect of age, testing site, shorter GAA repeat length, sex and ambulation status on progression. When we stratified the FARS, Z2 and Z3 by age (Table 3a), patients ≥ 18 had a slower two-year decline in FARS scores ($p=0.586$), Z2 ($p=0.059$) and Z3 ($p=0.150$). For this univariate analysis, this difference only approached statistical significance for Z2. As age is associated with other variables such as GAA repeat length, we also examined the effect of age in linear regression models accounting for testing site, sex, and shorter GAA repeat length (Table 3c). In such models, age was a significant predictor of the speed of progression, with younger patients changing faster. In contrast, shorter GAA repeat length was statistically significant only in predicting Z2 scores ($p=0.018$), and testing site did not significantly influence results in the FARS ($p=0.25$), Z2 ($p=0.81$) or Z3 ($p=0.58$) (Table 3c).

When we stratified FARS, Z2 and Z3 by sex (Table 3b), we found a substantial difference between male and female scores on the FARS. The average two-year FARS change across

both sexes was 6.2 ± 7.35 . However, the average FARS increase for women was 7.6 ± 7.4 and for men was 4.6 ± 7.4 ($p=0.029$). When we used linear regression analysis to assess the effect of sex with regards to testing site, age, and shorter GAA repeat length, the p value for sex in predicted FARS scores was $p=0.10$, which approaches statistical significance. To determine why the FARS scores were disparate, we analyzed each subscore of the FARS by sex (Table 4). Scores in females were higher than males in all categories except bulbar; however only the upper extremities subscore, which measures strength and coordination of the upper body, reached statistical significance ($p=0.022$).

We also examined the ability of these measures to capture progression in non-ambulatory patients. Neither FARS nor Z3 was affected by ambulation status (Table 5), although Z2 was affected in a statistically significant manner ($p=0.005$).

Discussion

This study demonstrates that the FARS, E-FARS, Z2 and Z3 all capture disease progression in FRDA. Individual performance measures, except PATA, also capture progression but were associated with much greater relative standard deviations. In addition, all of the FARS-related and composite-measure scores showed a substantially greater SD/mean ratio at one year than at two years. This suggests that studies designed to assess FRDA progression in unselected sub-populations will almost certainly require a two-year duration. However, one should use these numbers cautiously in creating sample size calculations. Data derived from natural history approaches are not always readily extrapolated to clinical trials, and some measures may be more affected by practice or placebo effects that are found in clinical trials.

The measures differed in their ability to capture disease progression and differed in potential biases. On average, the performance-measure composites were more linear over the two years than the FARS, suggesting that they are less likely to have ceiling or floor effects. In addition, the FARS and Z3 capture change in both ambulatory and non-ambulatory individuals. Since the Z2 combines the 9HPT (requiring fine coordination) and the T25FW (requiring ambulation), it cannot capture disease progression in individuals unable to perform either task (16 subjects at year two). This difficulty with the Z2 measure was not noted in simple examination of the mean rate of change, but was only revealed by regression analysis. In addition, the relation of change in Z2 to GAA repeat length differed from previous cross-sectional data and seemingly contradicted the known molecular basis of the disorder, with patients having shorter GAA repeats appearing to change faster. This most likely reflects a selection bias, as older patients with longer GAA repeats have reached the ceiling of the Z2 measure. Thus, the Z3 and FARS may be useful across all populations, whereas the Z2 is likely to be useful only among ambulatory patients and those who retain some arm function.

Past studies have suggested that the International Cooperative Ataxia Rating Scale captures more pronounced changes in ambulatory subjects [14]. However, the present data shows that changes in non-ambulatory subjects can be measured with the FARS and Z3, and to a lesser extent with the Z2. With these scales, non-ambulatory subjects can be included in therapeutic trials. The present results are also consistent with a previous longitudinal analysis of a smaller Australian cohort of patients with FRDA [15]. The rate of change in the Australian cohort was slightly faster than in our cohort, perhaps reflecting the longer GAA repeat length in that cohort or the high use of antioxidants in our cohort [16]. Still, both cohorts change substantially after losing ambulation ability, thus showing that such groups can be included in therapeutic trials.

While the present data show that most patients with FRDA can be assessed quantitatively, as needed for clinical trials, the data also define the groups of patients in whom change is fastest. These patients may represent ideal subjects for therapeutic trials of shorter duration. Age was

a primary factor in determining apparent rate of change, with children changing faster than adults. These observed changes are consistent with the observation that those who present with onset in childhood typically have more severe disease courses than those who present with onset in adulthood.

Based on the present data, the FARS may have a modest sex bias. This difference was statistically significant in stratifying by sex ($p=0.029$) but multivariate regression models did not confirm an effect of sex ($p=0.10$), possibly reflecting a type 2 error and the need for a larger sample size. The present data suggest that in the FARS exam, particularly in the upper extremities subscore, women change at a faster rate than men. There is no obvious explanation for this finding, as the men and women in the present study were similar in shorter-GAA-repeat length, age, and testing site. Previous work has suggested that female FRDA patients are at an increased risk of becoming dependent on assistive walking devices or wheelchairs [17]. Further research is required to determine if this is a true biological phenomenon or if selection bias is occurring across multiple measures in multiple disorders.

Although a large number of patients take anti-oxidants in an attempt to slow FRDA, we did not examine the effect of such treatments on disease progression. We have previously shown that there is a selection bias in anti-oxidant use in this cohort, with larger numbers of pediatric patients taking anti-oxidants such as Idebenone or Coenzyme Q10 [16]. However, if such antioxidants are efficacious, our results may under-represent the actual rate of disease progression in children.

The present work shows that the FARS, E-FARS, Z2 and Z3 are all effective measures of FRDA progression. The Z2 and Z3 both have relatively higher standard deviations, but measure change over time more linearly. The FARS may exhibit some sex bias, which requires further investigation. Z3 and FARS both capture changes in non-ambulatory subjects, while Z2 is less useful in these subjects. All of the measures have a lower SD/mean ratio over two-year periods, suggesting that smaller sample sizes will be required for clinical trials of longer durations. The present results help to establish norms for the FRDA population and can be used to guide sample-size calculations for future clinical trials.

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Table 1

Change in Measures over One and Two Year Periods

	Baseline to Year 1				Baseline to Year 2			
Measure	Mean	SD	Skewness	SD/ Mean	Mean	SD	Skewness	SD/ Mean
9HPT ⁻¹	-0.00087	0.002	-0.403	2.30	-0.0016	0.0024	0.094	1.50
T25FW ⁻¹	-0.0094	0.036	-1.3	3.83	-0.015	0.036	-2.6	2.40
LCLA	2.29	11.9	0.31	5.18	5.99	16.2	0.32	2.70
PATA	0.87	3.17	1.03	3.64	0.86	4.27	0.41	4.97
Z2	-0.17	0.45	-0.61	2.65	-0.32	0.47	-1.10	1.47
Z3	-0.23	0.58	-0.86	2.52	-0.48	0.66	-0.37	1.38
FDS	0.23	0.49	0.63	2.13	0.33	0.57	0.60	1.72
ADL	1.39	3.17	0.48	2.28	2.62	3.06	0.22	1.17
FARS	3.55	6.96	0.02	1.96	6.16	7.35	-0.16	1.19
E-FARS	5.51	8.77	0.01	1.59	8.93	8.87	0.04	0.99

SD: Standard deviation, 9HPT⁻¹: Reciprocal value of 9 hole peg test, 25FTW⁻¹: Reciprocal value of timed 25 foot walk, LCLA: Low-contrast letter acuity test, PATA: PATA speech test, Z2: Composite of z scores from 9HPT⁻¹ and 25FTW⁻¹, Z3: Composite of z scores from 9HPT⁻¹, 25FTW⁻¹ and LCLA, FDS: Functional Disability Scale, ADL: Activities of Daily Living, FARS: Friedreich Ataxia Rating Scale, E-FARS: Expanded FARS (ADL, FARS, and FDS scores added together)

Table 2

Friedreich Ataxia Rating Scale Changes by Subscore

Subscore	Baseline to Year			Baseline to Year 2		
	Mean	SD	Skewness	Mean	SD	Skewness
Bulbar	0.19	0.91	0.22	0.234	1.00	0.83
Upper	1.39	3.27	-0.17	2.27	3.81	-0.083
Lower	0.73	2.51	0.44	1.48	2.59	0.49
Peripheral	0.226	3.23	0.091	0.45	3.20	-0.079
Upright Stability	1.01	2.42	0.593	1.67	2.83	0.89

SD: Standard deviation

Table 3

Stratification of Change and Regression of Change

3a - Stratification of Change from Baseline to Year 2 by Age			
Age	FARS	Z2	Z3
Age ≥ 18	6.0 ± 7.4 N=101	-0.27 ± 0.39 N=92	-0.43 ± 0.58 N=81
Age < 18	7.2 ± 7.2 N=18	-0.47 ± 0.66 N=24	-0.66 ± 0.9 N=22
p value	p=0.586	p=0.059	p=0.150

3b - Stratification of Change from Baseline to Year 2 by Sex			
Sex	FARS	Z2	Z3
Men	4.6 ± 7.4 N=57	-0.33 ± 0.39 N=55	-0.42 ± 0.55 N=49
Women	7.6 ± 7.4 N=62	-0.31 ± 0.52 N=61	-0.58 ± 0.75 N=54
p value	p=0.029	p=0.818	p=0.402

3c - Linear Regression from Baseline to Year 2				
Measure	Age	Sex	Site	GAA
FARS	p=0.04	p=0.10	p=0.25	p=0.53
Z2	p=0.002	p=0.89	p=0.81	p=0.018
Z3	p=0.008	p=0.74	p=0.58	p=0.37

FARS: Friedreich Ataxia Rating Scale, Z2: Composite of z scores from 9HPT⁻¹ and 25FTW⁻¹, Z3: Composite of z scores from 9HPT⁻¹, 25FTW⁻¹ and LCLA, Site = site where testing was performed, GAA = length of shorter GAA triplet repeat, p: p-value

Table 4

Change in Friedreich Ataxia Rating Scale Subscore by Sex (Baseline to Year 2)

N=57 males 62 females	Sex	FARS change	SD	p value
Bulbar	M	0.31	1.04	p=0.451
	F	0.17	0.98	
Upper	M	1.4	4.0	p=0.022
	F	3.0	3.5	
Lower	M	1.2	2.3	p=0.292
	F	1.7	2.8	
Peripheral	M	0.13	3.2	p=0.310
	F	0.73	3.2	
Upright Stability	M	1.6	2.8	p=0.804
	F	1.73	2.9	

SD: Standard deviation, FARS: Friedreich Ataxia Rating Scale, p: p-value

Table 5

FARS, Z2 and Z3 Stratified by Ambulation (Baseline to Year 2)

Status	FARS	Z2	Z3
Ambulatory	5.3 ± 7.0 N=58	-.42 ± .57 N=66	-.49 ± .71 N=60
Non-Ambulatory	6.9 ± 7.6 N=61	-.18 ± .19 N=50	-.47 ± .60 N=43
p value	p=0.23	p=0.005	p=0.88

FARS: Friedreich Ataxia Rating Scale, Z2: Composite of z scores from 9HPT⁻¹ and 25FTW⁻¹, Z3: Composite of z scores from 9HPT⁻¹, 25FTW⁻¹ and LCLA, p: p-value