Original Investigation

A 22-Year Follow-up Study of Long-term Cardiac Outcome and Predictors of Survival in Friedreich Ataxia

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IMPORTANCE Friedreich ataxia (FRDA) is the most common genetic sensory ataxia, and myocardial involvement is a major determinant of survival.

OBJECTIVE To assess FRDA survival and cardiac outcome to adapt future therapeutic trials.

DESIGN, SETTING, AND PARTICIPANTS In a longitudinal follow-up study, all patients with genetically confirmed FRDA seen in the reference center and referred for cardiac evaluation (standard 12-lead electrocardiogram and transthoracic echocardiography) to the cardiology department were enrolled and followed up from April 27, 1990, to July 31, 2013. The setting was the French National Reference Center for Rare Diseases and the Department of Cardiology, Salpêtrière University Hospital, Paris, France. In total, 138 patients with FRDA were followed up. Among 133 patients homozygous for expanded GAA repeats, the mean (SD) age was 31 (10) years (age range, 11-62 years), with a mean (SD) age at disease onset of 16 (8) years (age range, 3-50 years) and a mean (SD) age at first wheelchair use of 26 (9) years (age range, 11-64 years). Cardiac hypertrophy was present in 57.9% (77 of 133), and electrocardiography was normal in 6.8% (9 of 133).

MAIN OUTCOMES AND MEASURES Long-term cardiac outcome and predictors of survival in FRDA.

RESULTS After a mean (SD) follow-up of 10.5 (5.5) years (range, 0.6-23.0 years), the 10-year survival rate was 88.5%. In 80.0% of patients (12 of 15), death was due to cardiac causes. Predictors of survival were a shorter GAA repeat length on the smaller allele of the frataxin gene (hazard ratio [HR], 1.85; 95% CI, 1.28-2.69), left ventricular ejection fraction (HR, 0.42; 95% CI, 0.20-0.89), and left ventricular mass index (HR, 1.19; 95% CI, 1.04-1.36). Two cardiac evolutions were distinguished with a group-based trajectory model, including a low-risk cardiac group (78.6% [81 of 103] with normal ejection fraction at baseline that declined slightly over time but remained within the normal range) and a high-risk cardiac group (21.4% [22 of 103] in which the ejection fraction progressively declined during follow-up). The patients with the worse cardiac evolution had longer GAA repeats. Neurological impairment was not predictive of cardiac change over time.

CONCLUSIONS AND RELEVANCE Survival in FRDA is determined by cardiac complications, which are dependent on the mutation (ie, the size of the expanded GAA repeat). Patients with progressive decline of the left ventricular ejection fraction had a worse prognosis. This finding demonstrates that cardiac follow-up is important in FRDA to identify individuals at risk for further cardiac complications.

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Friedreich ataxia (FRDA) is the most common autosomal recessive ataxia. The phenotype is reminiscent of mitochondrial disease, with cerebellar signs (ataxic gait, dysarthria, coordination difficulties, and ocular fixation instability), sensory neuropathy (sensory ataxia, weakness, and deep sensory loss), pyramidal signs (extensor plantar response and leg spasticity), visual and hearing impairment, and nonneurological features, such as hypertrophic cardiomyopathy and diabetes mellitus. The onset is around puberty, sometimes later in life, and, in rare cases, during early childhood.

Although the results of small studies have suggested that myocardial involvement is a major determinant of survival, to our knowledge, no large study has yet investigated survival, causes of death, and predictors of evolution in FRDA. Almost all patients with FRDA show abnormalities on the electrocardiogram,[1,2] and most show evidence of hypertrophic cardiomyopathy. Fibrosis on magnetic resonance imaging has been shown to be an early manifestation of cardiomyopathy in the absence of significant hypertrophy.[3] Clinical signs of heart involvement usually appear late in FRDA, but one study[4] reported an excess of cardiac deaths before age 40 years.

The mutated gene in FRDA, *FXN* (OMIM 606829), maps to the 9q13 chromosome[5] and encodes frataxin, a mitochondrial protein involved in the biosynthesis of iron-sulfur clusters. Most patients are homozygous for an expanded trinucleotide GAA repeat in the first intron of the *FXN* gene, whereas others are compound heterozygotes with an expanded GAA repeat and an *FXN* point mutation or deletion.[2,5,6] The expanded GAA repeat inhibits expression of the *FXN* gene through epigenetic mechanisms, resulting in reduced levels of frataxin. Longer repeats cause a greater loss of frataxin. Its level mostly depends on the length of the shorter of the 2 GAA repeat alleles.[6] Accordingly, a larger number of GAA repeats on the shorter allele is associated with earlier symptom onset, increased neurological severity, and more severe cardiomyopathy.[2,7-10] Impaired mitochondrial oxidative phosphorylation, deficient iron-sulfur cluster enzymes, and mitochondrial iron overload are observed in the myocardium of patients with FRDA as a consequence of the frataxin deficiency.[11-13] However, the correlation between residual frataxin levels and left ventricular (LV) hypertrophy and function remains poorly understood. Although the neurological condition deteriorates over time, the progression of cardiac disease is variable. In light of developments in the prevention and treatment of cardiomyopathy by gene therapy in a mouse model of FRDA,[14] we assessed survival and cardiac outcome in a large cohort of patients with FRDA. Our objectives were to describe survival and cardiomyopathy to identify predictors of poor cardiac evolution.

Methods

Study Design

We included clinical data from all patients with genetically confirmed FRDA seen from April 27, 1990, to July 31, 2013, in the French National Reference Center for Rare Diseases and referred for cardiac evaluation to the Department of Cardiology, Salpêtrière University Hospital, Paris, France. The Institut national de la santé et de la recherche médicale (INSERM) approved the study. Informed written consent was given in accord with the law and local ethical regulations. All patients gave consent for genetic and modifier studies. Fifty patients were included since 2010 as part of a prospective European FRDA registry (European Friedreich's Ataxia Consortium for Translational Studies; http://www.e-facts.eu),[7] which is coordinated by one of us (M.P.).

Information about events was gathered from September 1, 2012, to December 31, 2015, by direct examination, telephone, or mail. When contact with a patient or the family was not possible, the date of death was obtained from the French national registry of deaths.

Neurological examination was performed within 6 months of cardiac evaluation, including 2 neurological rating scales for ataxia. These were the International Cooperative Ataxia Rating Scale[15] (ICARS), with a maximum score of 100, and the Scale for the Assessment and Rating of Ataxia[16] (SARA), with a maximum score of 40.

Cardiac evaluation included clinical examination, standard 12-lead electrocardiography, and transthoracic echocardiography. Cardiac arrhythmia, heart failure, and stroke were recorded. Electrocardiograms were interpreted retrospectively by a cardiologist (L.L.) masked to the echocardiography results. An electrocardiogram was considered abnormal in the presence of T-wave inversion (≥0.1 mV) or flat T wave in at least 2 leads except for V1 or V2 in the absence of a bundle branch block. Transthoracic echocardiographic studies were performed using an initial device (Sigma 1; Kontron Instruments) and subsequently using other systems (Sequoia C256; Acuson and Vivid 7; General Electric Company). Left ventricular end diastolic diameter (LVEDD) and end systolic diameter (LVESD), LV end diastolic interventricular septal wall thickness (SWT), and posterior wall thickness (PWT) were measured using standard M-mode from a parasternal long-axis view.[17] Left ventricular contractility was evaluated by LV ejection fraction (LVEF) using the biapical Simpson disk method.[17] Systolic dysfunction was defined as LVEF below 50%. Calculated morphologic parameters included the ratio of SWT to PWT and relative wall thickness, defined as (SWT + PWT) / LVEDD.[18] Pathological concentric LV remodeling was defined by a relative wall thickness exceeding 0.42. Left ventricular mass was assessed using the following formula:

$$\text{LV mass} = 0.8 \times [1.04 \times (\text{LVEDD} + \text{PWT} + \text{SWT})^3 - \text{LVEDD}^3] + 0.6\ \text{g}.$$

LV mass was indexed to body surface area as an LV mass index (LVMI).[18] Because the patients were younger than 40 years, nomograms by Henry et al[19] were used to adjust thickness parameters for age and body surface area. Cardiac hypertrophy was defined when SWTs or PWTs exceeded the 95% predicted value for age and body surface area.[8] Mitral valve inflow was measured by Doppler to obtain the ratio of early to late diastolic flow velocity.

Statistical Analysis

Data are expressed as the mean (SD) and range for quantitative variables except where otherwise indicated. Relationships be-

tween continuous variables were evaluated by Pearson product moment correlation. Clinical and echocardiographic characteristics of patients with and without cardiac hypertrophy were compared using Pearson χ^2 test for qualitative variables and analysis of variance for quantitative variables. Survival was defined as the interval between the first cardiac visit and death or last news. Cox proportional hazards univariate analysis, followed by multivariable models with a stepwise procedure, were used to evaluate risk factors for death. Evolution of echocardiographic parameters was analyzed using linear mixed models, with time as both a fixed and random effect (*df* was estimated using approximation by Satterthwaite[20]).

To identify subgroups of participants exhibiting different trajectories of LVEF, we used a semiparametric mixture group-based trajectory model.[21] This models the link between time and a variable of interest as a polynomial relationship. For each trajectory group, the model defines the shape of the trajectory and the estimated proportion of the population belonging to the group. It also determines the probability of belonging to the different trajectory groups (called posterior membership probabilities) for each individual, with the highest probability group determining group assignment. To select the best fit, we ran models with 2 to 6 trajectories, with a base specification requiring all shapes to be quadratic, and selected the model with the largest significant trajectory order estimates and a maximized Bayesian information criterion. We calculated the mean individual posterior membership probabilities for each group to examine the model fit. Finally, baseline characteristics associated with the members of each trajectory group were compared using logistic regression analysis.

All reported *P* values are 2-tailed. A type I error rate of 5% was used. Analyses were performed with a statistical software package (SAS, version 9.3; SAS Institute Inc).

Results

We included 138 patients with genetically confirmed FRDA from 122 families. Five patients with heterozygous *FXN* point mutations were excluded from the statistical analysis to avoid introducing a severity bias. Among them, 4 had cardiac hypertrophy, 4 experienced no cardiac events during follow-up, and 1 patient underwent heart transplantation (eTable 1 and eTable 2 in the Supplement).

In total, 103 of 133 patients homozygous for expanded GAA repeats were evaluated at least twice. Overall, there were 498 cardiac evaluations, a median interval between 2 cardiac evaluations of 1.7 years (range, 0.3-19.8 years), and a median number of 4 (range 2-12) cardiac evaluations per patient. The neurological and cardiac characteristics of these 133 patients are listed in **Table 1**.

At the first cardiac visit, 3.0% (4 of 133) of the patients had dyspnea, 9.0% (12 of 133) had chest pain, and 9.8% (13 of 133) had palpitations, while no patients had signs of heart failure. Two patients had diabetes mellitus, 7 patients had hypertension, 6 patients had previous atrial fibrillation, and 1 patient had previous symptoms of heart failure.

Only 6.8% (9 of 133) of the patients had normal electrocardiograms, and 18.8% (25 of 133) had a right bundle branch block. The most common abnormal feature was the presence of abnormal repolarization (87.9% [116 of 132]), with negative (89.7% [104 of 116]) or flat (10.3% [12 of 116]) T wave in inferior (7.7% [9 of 116]), lateral (15.5% [18 of 116]), or both (16.3% [19 of 116]) leads. The mean (SD) heart rate was 76 (12) beats/min, and all patients were in sinus rhythm except for 2 who had atrial fibrillation. No patients had LVEFs less than 50%. Left ventricular hypertrophy was detected in 77 of 133 patients (57.9%), with SWTs or PWTs exceeding the 95% predicted value for age and body surface area, as previously defined. Among 133 patients, LVMI was significantly elevated in 52 (39.1%), including 22 men (LVMI >115 g/m^2) and 30 women (LVMI >95 g/m^2). Only 17 of 133 (12.8%) had severe cardiac hypertrophy, with SWT exceeding 15 mm. Among 56 patients with no cardiac hypertrophy, 18 (32.1%) had normal SWT or PWT.

Two-thirds of patients with normal echocardiography had abnormal T waves on electrocardiograms. This finding suggested myocardial involvement even without detectable hypertrophy.

There was a strong correlation between a shorter GAA repeat length and age at onset ($r = -0.61$, $P < .001$), as well as with the following parameters: SWT ($r = 0.24$, $P = .005$), LVEDD ($r = -0.32$, $P < .001$), transmitral A wave ($r = -0.27$, $P = .004$), and the ratio of early to late diastolic flow velocity ($r = 0.26$, $P = .007$). The length of the longer GAA repeat also correlated with age at onset ($r = -0.42$, $P < .001$), SWT ($r = 0.20$, $P = .02$), and PWT ($r = 0.21$, $P = .01$).

Overall, patients with cardiac hypertrophy were younger, had longer GAA repeats on both alleles, experienced earlier disease onset, and initiated wheelchair use at an earlier age. Fifty-four percent of patients with no cardiac hypertrophy had abnormal LV remodeling. Patients with cardiac hypertrophy had a higher ratio of early to late diastolic flow velocity, suggesting diastolic dysfunction. The LVEF was similar in the 2 groups with and without cardiac hypertrophy.

Survival Analysis

Among 133 patients, 15 (11.3%) died at a mean (SD) age of 39 (10) years (age range, 27-61 years) after a mean (SD) follow-up of 10.5 (5.5) years (range, 0.6-23.0 years) (**Figure 1**). Eight patients died of cardiovascular causes. Of those, 6 (age range, 27-49 years) died of progressive heart failure, and 2 had atrial fibrillation and progressive heart failure and died after cardioembolic stroke at ages 32 and 43 years. Two patients died of noncardiac causes and one of respiratory disease (at age 33 years), while the death of the other was from suicide (at age 28 years). Five deaths (age range, 33-61 years) were of unknown origin, but 4 of these 5 patients were known to have atrial fibrillation.

Cardiac events included supraventricular arrhythmias in 16.5% (22 of 133) of patients, LVEFs below 50% in 9.8% (13 of 133), and heart failure in 8.3% (11 of 133) (eTable 3 in the Supplement). One patient with a low LVEF received a prophylactic implantable defibrillator with no shock, and 1 patient had a pacemaker for bradyarrhythmia. In addition, 4 patients developed hypertension, and 9 patients had diabetes mellitus.

Table 1. Clinical and Echocardiographic Characteristics at Baseline of 133 Patients Having Friedreich Ataxia (FRDA) With and Without Cardiac Hypertrophy

Variable	All Patients With FRDA Homozygous for Expanded GAA Repeats (N = 133)	No Cardiac Hypertrophy (n = 56)	Cardiac Hypertrophy (n = 77)	*P* Value
Sex, No.				
Male	59	20	39	.08
Female	74	36	38	
Age at inclusion, mean (SD) [range], y	31 (10) [11-62]	34 (11) [13-62]	28 (9) [11-50]	<.001
Age at onset, mean (SD) [range], y	16 (8) [3-50]	19 (10) [3-50]	13 (6) [3-42]	<.001
Cerebellar score at first examination, mean (SD)				
ICARS	44 (24) (n = 44)	45 (27) (n = 22)	43 (20) (n = 22)	NA
SARA	22 (8) (n = 11)	23 (6) (n = 5)	22 (9) (n = 6)	NA
Age at first wheelchair use, mean (SD) [range], y	26 (9) [11-64] (n = 98)	31 (11) [11-64]	23 (7) [11-40]	<.001
Shorter GAA repeat, mean (SD)	609 (241)	540 (247)	659 (224)	.004
Longer GAA repeat, mean (SD)	879 (237)	815 (250)	925 (219)	.008
Cardiac Parameters				
Body surface area, mean (SD)	1.70 (0.19)	1.73 (0.19)	1.68 (0.18)	.10
Septal wall thickness, mean (SD), mm	11.8 (2.8)	9.7 (1.4)	13.3 (2.5)	<.001
Posterior wall thickness, mean (SD), mm	11.0 (2.4)	9.1 (1.2)	12.4 (2.2)	<.001
Relative wall thickness, mean (SD)	0.54 (0.15)	0.43 (0.07)	0.63 (0.13)	<.001
Patients with relative wall thickness ≥0.42, No. (%)	107 (80.5)	30 (53.6)	77 (100)	<.001
Left ventricular end diastolic diameter, mean (SD), mm	42.7 (4.6)	44.3 (4.5)	41.6 (4.4)	<.001
Left ventricular end systolic diameter, mean (SD), mm	25.1 (4.8)	26.3 (5.1)	24.4 (4.5)	.03
Left ventricular ejection fraction, mean (SD), %	68 (7)	67 (7)	68 (7)	.22
Left ventricular mass index, mean (SD), g/m^2	103 (31)	81 (13)	119 (31)	<.001
Peak early wave, mean (SD), cm/s	72 (15) (n = 103)	73 (22) (n = 47)	71 (13) (n = 66)	.40
Peak late wave, mean (SD), cm/s	51 (15) (n = 111)	66 (13) (n = 47)	55 (22) (n = 65)	.001
Ratio of early to late diastolic flow velocity, mean (SD)	1.5 (0.6) (n = 112)	1.3 (0.5) (n = 47)	1.7 (0.6) (n = 65)	.001
Medications, No. of Patients				
β-Blocker	26	8	18	NA
Angiotensin-converting enzyme inhibitor	5	3	2	NA
Furosemide	1	1	0	NA
Digoxin	1	0	1	NA
Amiodarone	3	1	2	NA
Flecainide acetate	1	1	0	NA
Anticoagulant	2	0	2	NA
Aspirin	4	3	1	NA

Abbreviations: ICARS, International Cooperative Ataxia Rating Scale; NA, not applicable (not compared statistically because of small sample size); SARA, Scale for the Assessment and Rating of Ataxia.

Patients with hypertrophy had more cardiac events than patients without hypertrophy, with 16 vs 6 having supraventricular arrhythmia (*P* = .12), 11 vs 2 having LVEF less than 50% (*P* = .04), 10 vs 1 having episodes of heart failure (*P* = .03), and death occurring in 12 vs 3 (*P* = .06). For 18 patients with normal hearts, neither death nor cardiac events were reported.

In the univariate analysis, mortality was associated with longer GAA repeats on both alleles, earlier age at onset, higher SWT and LVESD, LVMI, and smaller LVEF (**Table 2**). In the multivariable analysis, independent predictors of mortality were the length of the shorter GAA repeat (hazard ratio [HR], 1.85; 95% CI, 1.28-2.69 per 100 additional repeats), LVEF (HR, 0.42; 95% CI, 0.20-0.89 per 10% decrease), and LVMI (HR, 1.19; 95% CI, 1.04-1.36 per increase of 10 g/m^2).

We estimated the neurological evolution of 69 patients. Among 34 patients, the mean (SD) SARA score worsened from 24 (7) (range, 9-38) to 27 (6) (range, 13-36) after a mean (SD) follow-up of 4 (2) years. Among 55 patients, the mean (SD) ICARS score worsened from 54 (20) (range, 7-90) to 62 (20) (range, 10-98). The SARA score increased a mean (SD) of 4 (5) points (*P* < .001), and the ICARS score increased a mean (SD) of 8 (10) points (*P* < .001). Neither the SARA score nor the ICARS score at baseline was predictive of cardiac change over time.

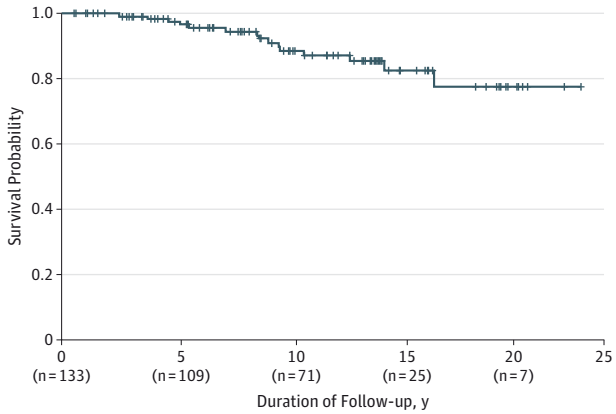
All cardiac parameters evolved over time, with a mean (SE) decrease in LVEF of 0.68% (0.10%) ($P < .001$) and with the mean (SE) decreases in SWT of −0.055 (0.021) mm ($P = .01$) and PWT of −0.11 (0.02) mm ($P < .001$). The mean (SE) increases were 0.27 (0.05) mm ($P < .001$) for LVEDD and 0.33 (0.06) mm ($P < .001$) for LVESD. The LVMI decreased by a mean (SE) of −0.42 (0.21) g/m^2 ($P = .05$).

Trajectory Analysis

The best-fitting model included 2 trajectories: a large low-risk group (78.6% [81 of 103]) with normal LVEF at baseline that declined slightly over time but remained in the normal range and a smaller high-risk group (21.4% [22 of 103]) with a progressively decreasing LVEF (**Figure 2**). The mean (SE) LVEFs at inclusion were 70% (6%) in the low-risk group and 61% (5%) in the high-risk group ($P < .001$). The mean posterior probabilities that a participant belonged to his or her assigned group were above 0.5, indicating a good model fit. The probability of belonging to the high-risk group depended on the length of the shorter GAA repeat, age at onset, and LVESD at inclusion (**Table 3**). In the multivariable analysis, only a shorter GAA repeat length and LVESD remained predictors of a decreased LVEF. The LVESD and LVEF were significantly correlated at baseline ($r = −0.55$, $P < .001$).

The initiation of wheelchair use as an indicator of severity did not differ between the 2 trajectory groups, with the mean (SD) age at wheelchair use being 26.6 (9.5) years for normal LVEF vs 22.4 (8.6) years for low LVEF ($P = .94$). The time between the onset of disease and wheelchair use did not indicate a faster neurological evolution in the group with a poor cardiac trajectory, with the mean (SD) periods being 10.0 (6.0) years for normal LVEF vs 7.4 (5.7) years for low LVEF ($P = .17$).

Figure 1. Survival Curve in 133 Patients With Friedreich Ataxia



The mean age at death was 39 years, and survival was 88.7% (118 of 133) after 10 years of follow-up.

Discussion

To our knowledge, this study is the first survival analysis and long-term follow-up of a large cohort of patients with FRDA. The 10-year survival rate of 88.5% indicates a better prognosis than was previously reported.[17] We found that the mean age at death was 39 years, which was slightly older than previously reported.[2] We confirm that the major causes of mortality in patients with FRDA are cardiovascular, primarily progressive heart failure, with a low LVEF. When the cause of death was classified as unknown, 4 of 5 patients had previous cardiac events, so these deaths could be attributed to cardiac causes.

An important finding of this study is that the length of GAA repeats on both alleles of the *FXN* gene (ie, the residual amount of frataxin) is the best predictor of mortality in FRDA. The 2 other independent predictors of mortality were LVEF (reflecting systolic function) and LVMI (reflecting hypertrophy).

As previously reported,[22-24] we found that 57.9% (77 of 133) of patients had moderate cardiac concentric hypertrophy, with a small left ventricle without obstruction. Hypertrophy is mostly dependent on the size of the shorter GAA repeat,[7,23,24] but the length of the longer GAA repeat also correlated with cardiac wall thickness. The weak relationship suggests that additional factors modify cardiac phenotypic expression. Several definitions of hypertrophy are used in the literature.[25] Thirty-nine percent of our patients had hypertrophy based on LVMI. We used nomograms by Henry

Table 2. Survival Analysis in Friedreich Ataxia and Factors Influencing Survival[a]

	Univariate Analysis		Multivariable Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex	1.33 (0.48-3.72)	.58	NA	NA
Age at onset	0.81 (0.72-0.92)	.001	NA	NA
Age at inclusion	1.02 (0.97-1.07)	.49	NA	NA
Shorter GAA repeat	1.90 (1.39-2.61)	<.001	1.85 (1.28-2.69)	.001
Longer GAA repeat	1.07 (0.85-1.36)	.55	NA	NA
Septal wall thickness	1.22 (1.05-1.41)	.009	NA	NA
Posterior wall thickness	1.12 (0.94-1.33)	.20	NA	NA
Left ventricular end diastolic diameter	1.09 (0.97-1.22)	.13	NA	NA
Left ventricular end systolic diameter	1.16 (1.05-1.28)	.003	NA	NA
Left ventricular ejection fraction	0.28 (0.13-0.62)	.002	0.42 (0.20-0.89)	.02
Left ventricular mass index	1.17 (1.04-1.32)	.009	1.19 (1.04-1.36)	.01
Cardiac hypertrophy	2.05 (0.57-7.34)	.27	NA	NA

Abbreviations: HR, hazard ratio; NA, not applicable.

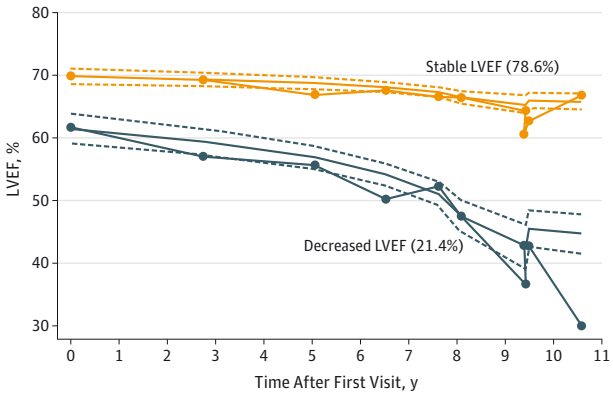
[a] The HRs are expressed per unit increase except for the GAA repeat (per 100 additional repeats), left ventricular ejection fraction (per 10% decrease), and left ventricular mass index (per increase of 10 g/m^2).

et al[19] because morphologic parameters are influenced by age and body surface area. Although this method might overestimate the degree of hypertrophy, it was found to be a good compromise between magnetic resonance imaging and echocardiographic categorization in the Mitochondrial Protection With Idebenone in Cardiac or Neurological Outcome (MICONOS) study.[26] Patients with hypertrophy had a worse prognosis and more cardiac events than patients without hypertrophy, but survival was similar despite a follow-up of 10 years, which is perhaps too short to produce a sufficient number of events in each group. In frataxin cardiac conditional knockout mice, hypertrophy is followed by dilated cardiomyopathy, which appears in parallel with mitochondrial respiratory chain dysfunction and iron accumulation.[27] In FRDA, cardiac involvement may progress to LV systolic dysfunction and heart failure. Two patients herein had severe dilated cardiomyopathy at ages 16 and 23 years. We observed a small decrease in LVEF, suggesting that cardiac function deteriorated slightly with time as previously shown,[28] and 21.4% (22 of 103) of patients herein developed significant alterations of LVEF. Evolution of LVEF depended on the size of the shorter GAA repeat and was independent of cardiac hypertrophy. We observed a regression of hypertrophy over time and an increase in the size of the left ventricle. Previous reports suggested contradictory cardiac changes over time, with either an increase[29] or a decrease[30] in hypertrophy.

As recommended,[31] cardiac follow-up in FRDA is necessary to identify early systolic LV dysfunction because clinical signs of cardiac dysfunction develop only later in the course of the disease. New echocardiography techniques, such as speckle tracking imaging, can detect alterations of contractility before a decreased LVEF.[23-25] Follow-up studies will be necessary to evaluate the usefulness of these new techniques in patients with FRDA.

Until specifically tailored treatments are developed, early treatment of cardiomyopathy by β-blockers, angiotensin-converting enzyme inhibitors, or antagonists of mineralocorticoid receptors should be proposed in patients with LVEF below 50% because of the expected progression of cardiac involvement.[31] However, controlled studies are necessary to evaluate whether earlier cardiac intervention can modify the

Figure 2. Trajectory Groups of Left Ventricular Ejection Fraction During Follow-up in 103 Patients With Friedreich Ataxia



Trajectories of left ventricular ejection fraction (LVEF) during follow-up (bold lines) were calculated using the model's coefficient estimates and 95% CIs (dotted lines). Two cardiac evolutions were distinguished, including a low-risk cardiac group (78.6% [81 of 103]), with a normal ejection fraction at baseline that declined slightly over time but remained in the normal range, and a high-risk cardiac group (21.4% [22 of 103]), which started with a lower ejection fraction and had a progressively decreasing ejection fraction.

Table 3. Characteristics of Trajectory Groups Among 103 Patients Having Friedreich Ataxia With at Least 2 Follow-up Visits[a]

	Trajectory Group		Univariate Analysis		Multivariable Analysis	
Variable	Stable LVEF (n = 81)	Decreased LVEF (n = 22)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female sex, No. (%)	46 (56.8)	10 (45.5)	1.58 (0.61-4.07)	.35	NA	NA
Age at inclusion, mean (SD), y	31 (10)	27 (8)	0.96 (0.91-1.01)	.13	NA	NA
Age at onset, mean (SD), y	16 (8)	12 (6)	0.91 (0.83-0.99)	.04	NA	NA
Age at first wheelchair use, mean (SD), y	26.6 (9.5)	22.6 (8.7)	0.94 (0.89-1.01)	.10	NA	NA
Duration until first wheelchair use, mean (SD), y	7.4 (5.7)	10.0 (6.0)	1.08 (0.98-1.20)	.17	NA	NA
Shorter GAA repeat, mean (SD)	605 (220)	758 (276)	1.37 (1.08-1.74)	.01	1.41 (1.08-1.83)	.01
Longer GAA repeat, mean (SD)	895 (219)	967 (280)	1.15 (0.93-1.43)	.20	NA	NA
Left ventricular end diastolic diameter, mean (SD), mm	42.1 (4.4)	43.6 (4.6)	1.08 (0.97-1.20)	.16	NA	NA
Left ventricular end systolic diameter, mean (SD), mm	23.9 (4.2)	28.5 (4.9)	1.23 (1.10-1.37)	<.001	1.26 (1.11-1.43)	<.001
Septal wall thickness, mean (SD), mm	11.9 (2.8)	11.8 (2.3)	0.98 (0.82-1.18)	.85	NA	NA
Posterior wall thickness, mean (SD), mm	11.3 (2.6)	10.6 (2.1)	0.88 (0.72-1.09)	.24	NA	NA
Left ventricular mass index, mean (SD), g/m^2	105 (32)	103 (27)	1.00 (0.98-1.01)	.72	NA	NA

Abbreviations: LVEF, left ventricular ejection fraction; NA, not applicable; OR, odds ratio.

[a] The ORs are expressed per unit increase except for the GAA repeat (per 100 additional repeats).

progression of cardiomyopathy in FRDA. Recently, a heart conditional *Fxn* knockout mouse model, which develops rapidly fatal cardiomyopathy, was rescued by administration of a frataxin-expressing viral vector after the onset of heart failure, with complete reversal of cardiomyopathy at the functional, cellular, and molecular levels.[14] This finding suggests that gene therapy may be a promising approach to treat cardiomyopathy in patients with FRDA and a low LVEF.

Our study had some limitations. Recruitment at our center mainly comprises adults, although 10 of 133 patients (7.5%) herein were younger than 18 years at baseline. However, age at onset was younger than 18 years for 94 of 133 patients (70.7%). We could have missed patients with early onset and severe evolution who did not come to our attention. Therefore, the findings can be generalized only to adults with FRDA.

We were unable to correlate evolution of neurological scores to cardiac measures. However, we showed that SARA scores at baseline were not predictive of survival, and age at first wheelchair use was not earlier in the worse cardiac trajectory group.

Idebenone has been identified as a potential treatment for FRDA, with a possible effect on cardiac disease.[26] Forty patients herein received idebenone at baseline, but intermittent use and incomplete prescription records prevented our assessment of the effect of idebenone on longitudinal cardiac outcome.

Conclusions

Survival is shortened in FRDA as a result of cardiac complications. We identified a low-risk cardiac group (78.6% [81 of 103]) that included most patients and a high-risk cardiac group (21.4% [22 of 103]) with a progressively decreasing LVEF. This finding demonstrates the importance of cardiac follow-up in FRDA and the necessity for patient stratification in therapeutic trials.

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