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Cross-Sectional Analysis of Electrocardiograms in a Large Heterogeneous Cohort of Friedreich Ataxia Subjects

Kimberly A. Schadt, MSN[1,2], **Lisa S. Friedman, MSN**[1,2], **Sean R. Regner, BS**[1,2], **George E. Mark, MD**[3], **David R. Lynch, MD, PhD**[1,2], and **Kimberly Y. Lin, MD**[4]

[1]Department of Pediatrics, Division of Neurology, Children's Hospital of Philadelphia, Pennsylvania

[2]Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Cardiology, Cooper University Hospital, Camden, New Jersey

[4]Department of Pediatrics, Division of Cardiology, Children's Hospital of Philadelphia, Pennsylvania

Abstract

Electrocardiographic (ECG) findings in Friedreich ataxia and their relation to disease characteristics have not been well described. In this retrospective cross-sectional study, we reviewed baseline ECGs from 239 children and adults with Friedreich ataxia. ECG abnormalities —assessed in relation to participant age, sex, shorter GAA triplet repeat length, age of disease onset, and functional disability score—were found in 90% of subjects, including nonspecific ST-T wave changes (53%), right axis deviation (32%), left ventricular hypertrophy (19%) and right ventricular hypertrophy (13%). Female sex and shorter GAA repeat lengths were associated with a normal ECG ($P = .004$ and $P = .003$). Males and those of younger age were more likely to show ventricular hypertrophy ($P = .006$ and $P = .026$ for left ventricular hypertrophy and $P < .001$ and $P = .001$ for right). Neurologic status as measured by the functional disability score did not predict ECG abnormalities.

Keywords

axis deviation; cardiac abnormalities; electrocardiogram; Friedreich ataxia; ventricular hypertrophy

Corresponding Author: Dr David R. Lynch, Children's Hospital of Philadelphia, Department of Neurology, Abramson Research Center, Room 502, 3615 Civic Center Blvd, Philadelphia, PA 19104; Phone: 215-590-2242; Fax: 215-590-3779; lynchd@mail.med.upenn.edu.

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Introduction

Friedreich ataxia is an autosomal recessive, multisystem, neurodegenerative disorder caused most commonly by guanine-adenine-adenine (GAA) trinucleotide repeat expansions in both alleles of the *FXN* gene.[1] These intronic expansions lead to decreased levels of the mitochondrial protein frataxin, ultimately causing mitochondrial dysfunction with abnormalities in iron homeostasis and potentially free radical regulation.[2,3] This malfunction may contribute to cellular hypertrophy, myocardial fibrosis, and necrosis.[4,5] Although disease features typically include progressive ataxia, areflexia, dysarthria, and sensory loss, abnormalities including insulin resistance, scoliosis, and cardiac hypertrophy remain variable.[6]

Cardiac abnormalities among individuals with Friedreich ataxia have been noted since the original description of the disease.[7,8] Manifestations frequently include electrophysiological disturbances and cardiomyopathy, most commonly hypertrophic, as opposed to dilated or restrictive, and classically marked by left ventricular hypertrophy. These cardinal features have historically been detected by nonspecific electrocardiographic (ECG) abnormalities and recognition of markers consistent with left ventricular hypertrophy on noninvasive echocardiographic imaging.[9] Cardiac dysfunction remains the major cause of death among individuals with Friedreich ataxia.[10]

Between 30% to 90% of individuals with Friedreich ataxia have ECG abnormalities that include nonspecific ST-T wave abnormalities, ventricular hypertrophy, or right axis deviation.[8,11,12] Other abnormalities include a short PR interval in up to 24% of patients[9,12,13] and interatrial block in up to 48% of patients.[14] Most of these have been identified only in modest-size cohorts. The largest known study examined 114 patients with Friedreich ataxia in the era before genetic testing, with 75.4% having an abnormal ECG tracing.[12] Eighty percent of patients with an abnormal ECG had nonspecific T-wave changes. Other commonly reported abnormalities included right axis deviation, right ventricular hypertrophy, and left ventricular hypertrophy.

The cardiac manifestations of Friedreich ataxia do not always correlate with severity of neurologic disease. A longitudinal review of cardiac data from a pediatric cohort of Friedreich ataxia patients showed no relationship between ambulatory status or GAA repeat length and cardiac morphology and function.[15] Our recent evaluation of an overlapping cohort of patients with Friedreich ataxia found that the functional disability score, a measure of neurologic disease status, did not predict echocardiographic abnormalities accounting for GAA repeat length.[16] Interestingly, in the same study, sex was the most consistent predictor of echocardiographic measurements of cardiac hypertrophy; GAA repeat length and age only predicted interventricular septal thickness in diastole. However, Bit-Avragim and colleagues showed that GAA repeat length was significantly associated with degree of left ventricular hypertrophy, as determined by two different echocardiographic measures.[17]

In this cross-sectional study, we evaluated 239 ECGs from a diverse Friedreich ataxia cohort to better characterize common ECG abnormalities. We hypothesized that ECG abnormalities in patients with Friedreich ataxia, particularly left ventricular hypertrophy, reflect sex and GAA repeat length but not the extent of neurologic disease as measured by functional disability score.

Methods

Subject Recruitment

The Institutional Review Board at the Children's Hospital of Philadelphia approved all protocols. Study participants were recruited during their clinical appointment at the Children's Hospital of Philadelphia or through study advertisement with the Friedreich Ataxia Research Alliance as part of a large, retrospective study to collect serial cardiac records on patients with Friedreich ataxia.[10,16] We enrolled 332 subjects, including both pediatric and adult participants with varying disease phenotypes and stages of disease progression. The only criterion for inclusion was a confirmed clinical or genetic diagnosis of Friedreich ataxia. Of the 332 participants enrolled, 243 provided at least one electrocardiogram.

A board-certified cardiologist blinded to participants' clinical course and disease phenotype (except for age and sex) independently reviewed the most recent ECG from the 243 subjects who provided them. The ECGs were classified as physiologically normal or abnormal on the basis of the reader's judgment and coded for rhythm, rate, axis, intervals, presence of conduction disturbance, and presence of atrial or ventricular hypertrophy. ECGs were excluded if the tracings were of insufficient quality or if the participant was in an abnormal atrial or ventricular rhythm. In total, 4 ECGs were excluded, 3 for poor quality and 1 for atrial fibrillation. To determine ECG features for both children and adults, ECGs were evaluated using specific criteria (Tables 1 and 2).

Statistics

Statistical analysis was performed using STATA SE Version 11.1 (StataCorp, College Station, Texas), including summary statistics, correlations, analysis of variance, and logistic and linear regression, to analyze the relationship between ECG features and GAA repeat length, age of disease onset, functional disability score (a measure of neurologic impairment scored from 0 to 6), age, and sex.

Results

Participant Demographics

Fifty-six percent of the study participants were female. Mean age at study participation was 23.8 ± 14.3 years (range, 2 years to 75 years). Mean age at onset of disease was 12.5 ± 10.1 years. One-hundred eighty-four (79%) participants had genetic confirmation of Friedreich ataxia. Of these, 5 (3%) carried a point mutation in conjunction with an expanded GAA repeat. The mean shorter GAA length for those with 2 expansions was 631 ± 221 repeats. Mean functional disability score was 3.9 ± 1.4, equivalent to ambulatory assistance with a cane or walker.

ECG Results

The data were generally normally distributed, and thus were analyzed using parametric statistical methods. Of 239 baseline ECGs, 215 (90%) had at least one abnormality identified (Table 3). Sinus rhythm was required for inclusion; 12participants (5.1%) had sinus tachycardia, 6 (2.5%) demonstrated sinus bradycardia, and 37 (15.5%) showed heart rate variability with respiration (also referred to as sinus arrhythmia). Nonspecific ST-T wave abnormalities, including ST-segment depression or elevation, flattening of the T wave, or T-wave inversion, were the most common abnormality observed in 127 (53.1%) participants. The other most frequent findings included right axis deviation (32%), left ventricular hypertrophy (19%), and right ventricular hypertrophy (13%).

The average heart rate in the cohort was 79.9 ± 13.7 bpm (range, 41 bpm to 131 bpm); as expected, lower age correlated with higher heart rate ($P = .003$, $r = -0.2$). Other intervals were similarly within normal limits, with exceptions noted in Table 3. Average PR interval was 137.2 ± 20.9 msec, average QRS interval 84.7 ± 14.6 msec, and average corrected QT interval 422.6 ± 23.7 msec.

Relation to Participant and Disease Features

The most common ECG finding of nonspecific ST-T wave abnormalities was not significantly different between males (45%) and females (54%). Likewise, right axis deviation was evenly distributed among males (34%) and females (31%). In contrast, left axis deviation 8% vs. <1%, $P = .005$), left ventricular hypertrophy (27% vs. 13%, $P = .005$), and right ventricular hypertrophy (23% vs. 5%, $P < .001$) were significantly more common in males compared with females. When classifying ECG findings by age category, compared with pediatric participants, surprisingly few participants older than 18 years of age had evidence of ventricular hypertrophy (Table 4).

By logistic regression analysis, age, sex, and markers of disease severity (i.e., functional disability score, GAA repeat length, and age of disease onset) did not predict most ECG abnormalities (data not shown). However, ventricular hypertrophy and axis deviations were associated with several notable participant and disease characteristics (Table 5). When controlling for age and GAA repeat length, males were more likely than females to have right ventricular hypertrophy (odds ratio [OR], 14.9;; 95% confidence interval [CI], 3.7–60.l). Younger age (OR 0.8; 95% CI, 0.7–0.9) and GAA repeat length (OR 1.004; 95% CI, 1.0001–1.0083) also had statistically significant associations with right ventricular hypertrophy; only age ($P = .045$; OR, 0.86; 95% CI, 0.74–0.99) showed an association in those whose right ventricular hypertrophy also showed a strain pattern. Likewise, males were more likely than females to have left ventricular hypertrophy (OR 3.0; 95% CI, 1.4–6.7); this association persisted in those who displayed left ventricular hypertrophy with strain ($P = .009$ for males and left ventricular hypertrophy with strain; OR 3.1; 95% CI, 1.3–7.0). Younger age had an association with left ventricular hypertrophy (OR 0.9; 95% CI, 0.91–0.99) that did not persist in those only showing left ventricular hypertrophy with strain ($P = .155$ for age and left ventricular hypertrophy with strain). Younger age (OR 0.96; 95% CI, 0.92–0.99) also predicted right axis deviation, while male sex (OR 9.6; 95% CI, 1.1–84.5) predicted left axis deviation. Those of female sex and individuals with shorter GAA repeat lengths were more likely to have a normal ECG (OR 0.085; 95% CI, 0.02–0.45, and OR 0.99; 95% CI 0.992–0.998, respectively).

When age of disease onset was substituted for GAA repeat length in our multivariate regression model as a marker of genetic severity, the findings were nearly identical. The only exceptions noted were that age of disease onset was not associated with presence of right ventricular hypertrophy ($P = .586$) whereas GAA repeat length was, and younger age of disease onset was weakly associated with presence of right axis deviation ($P = .043$; OR 0.92; 95% CI, 0.85–1.00), whereas GAA repeat length was not. As with GAA repeat length, older age of disease onset was also associated with normal ECG ($P = .015$; OR 1.1; 95% CI, 1.01–1.13).

When functional disability score was substituted for GAA repeat length in our multivariate regression model as a marker of disease severity, higher functional disability score showed a statistical association with the presence of right axis deviation ($P = .016$; OR 1.4; 95% CI, 1.06–1.76). However, this variable did not predict left ventricular hypertrophy, right ventricular hypertrophy, left axis deviation, ST-T changes, or an overall normal ECG.

Discussion

Our study expands the current knowledge of ECG abnormalities in Friedreich ataxia by examining a larger, more diverse cohort in the era of genetic testing. As expected, a significant number of individuals had ECG abnormalities. Thus, ECG irregularities remain a simple feature directing one toward the diagnosis of Friedreich ataxia in equivocal individuals. Most of the previously reported ECG anomalies in Friedreich ataxia were reproduced in the present study. These include the relative number of participants with abnormal ECGs, ventricular hypertrophy, and the disproportionate amount of right axis deviation and right ventricular hypertrophy.[8, 9, 12] However, this study did not identify the previously reported finding of short PR interval among patients with Friedreich ataxia.[12] Additionally, we did not systematically assess for the presence of interatrial block.

The frequency of right axis deviation observed on ECG remains disproportionate when one considers the relative infrequency of right ventricular hypertrophy. Other causes of right axis deviation include chronic pulmonary disease, pulmonary embolus, anterolateral myocardial infarction, left posterior hemiblock, septal defects, and Wolff-Parkinson-White syndrome; all are uncommon among the population of individuals with Friedreich ataxia. Furthermore, clinical evaluation of Friedreich ataxia primarily focuses on identification of left ventricular hypertrophy as opposed to right ventricular hypertrophy. Thus, the significance of amplified right axis deviation observations remains unclear.

As in the general Friedreich ataxia population, males in our cohort were more likely to have ECG evidence of ventricular hypertrophy, even when accounting for sex differences in ECG interpretation. Conversely, females were more likely to have a normal ECG. Perhaps our most interesting findings are the associations of ECG features with specific markers of disease severity. Normal ECGs were found in participants with shorter GAA repeat lengths, and were not associated with age. This suggests that the presence of a normal ECG is a marker of less severe biochemical disease and is a relatively static event. ST-T wave changes were similarly stagnant and marginally related to age of disease onset.

Relationships of markers of disease severity to ventricular hypertrophy and axis deviation were more complex. Except for right ventricular hypertrophy, these were not predicted by GAA repeat length, suggesting that axis deviations and left ventricular hypertrophy are sensitive measures of the Friedreich ataxia phenotype. In addition, the relation of ECG abnormalities to participant age was modest. Older participants had less ventricular hypertrophy than younger ones. This may be explained in 2 ways. First, if there was an insufficient statistical correction for the shorter GAA repeat length of participants with an older age of onset, this would lead to an apparent decrease in hypertrophy when analyzed in a cross-sectional cohort. Second, perhaps there is a decrease in ventricular hypertrophy by ECG over disease course, occurring in participants who become fibrotic. This could be due to regression of myocardial hypertrophy, or to decreased voltage produced by a weakened, fibrotic ventricle. Although serial analysis is clearly needed to confirm the second possibility, this has direct clinical implications. It suggests that serial ECGs may be unlikely to show clinically meaningful increases in hypertrophy, as the hypertrophy may have already been at or near its peak by time of disease diagnosis. Instead, ECG may be more important for identifying a loss of hypertrophy consistent with progression to fibrosis, which occurs later in disease progression. In addition, our overall model suggests that age, sex, age of onset, and GAA repeat length only partially explain ECG features. This insinuates that other genes may be important in modulating cardiac disease in Friedreich ataxia.[18]

As with all retrospective studies, the present study is limited by the possibility of selection bias. In addition, the data contain an amalgamation of routine ECGs as well as those

performed symptomatically. Similarly, ECGs can be altered by pharmacologic administration; however, it is not known which medications participants were taking at the time of the ECG. In addition, 21% of individuals in this study lacked genetic confirmation of disease. However, this is unlikely to alter data patterns, as the clinical diagnosis of Friedreich ataxia has been secure since the publication of Harding's criteria.[12] Furthermore, overall selection bias is unlikely to markedly affect the interpretation, as most of the results match those obtained with other smaller cohorts. In fact, the size of our cohort and the inclusion of both pediatric and adult participants add credence to those previously published series. Future studies that examine the correlation of ECG findings with concurrent clinical, echocardiographic, and magnetic resonance imaging data would help validate the clinical utility of these observations. Longitudinal follow-up data would determine whether ECG can assist in early diagnosis of Friedreich ataxia-associated cardiomyopathy, aid in its prognosis, or elucidate the underlying pathophysiological processes.

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Table 1

Electrocardiogram Criteria in Pediatric Subjects

Electrocardiogram Feature	Criteria[19]
Right atrial enlargement	P wave >2.5 mV in leads II, III, or aVF
Left atrial enlargement	P wave >0.08 sec in leads II, III, or aVF
Right ventricular hypertrophy	R wave >95%ile in V_1, or S wave >95%ile in V_6, or rsR′ in V_1 and V_2 without QRS widening, or qR in V_1 and V_2
Left ventricular hypertrophy	S wave >95%ile normal in V_1, or R wave >95%ile in V_6
Bundle branch block	QRS >0.12 sec
Right axis deviation	>10 degrees
Left axis deviation	>−30 degrees
Intraventricular conduction delay	QRS >0.12 sec and without RBBB or LBBB pattern
Non-specific ST-T changes	ST-segment depression or elevation (leads I, aVL, V_4–V_6), flattening of the T wave (leads I, aVR, aVL, V_5, V_6), or T-wave inversion (I, V_2–V_4)
Strain	Down-sloping convex ST-segment depression (≥0.1 mV) with an inverted asymmetrical T-wave opposite to the QRS axis. In LVH w/strain these changes were seen in the left precordial leads, V_5 and/or V_6. In RVH w/strain these changes were seen in the right precordial leads, V_1–V_3.

Abbreviations: LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RVH, right ventricular hypertrophy.

Table 2

Electrocardiogram Criteria in Adult Subjects

Electrocardiogram Feature	Criteria
Right atrial enlargement	P wave >2.5 mV in leads II, III, or aVF
Left atrial enlargement	P wave> 0.12 sec in leads II, III, or aVF, or P wave> 0.04 sec and −1mV (negative deflection) in V_1
Right ventricular hypertrophy	R wave >6mV or rsR′ >0mV in V_1, or S wave >7 mV in V_5 or V_6, or R wave in V1 + S wave in V_6 >10mV
Left ventricular hypertrophy	R wave > 11mV in aVL, or R wave > 25mV in V_5 or V_6, or R wave in V_6 + S wave in V_1 >35mV, or S wave in V_3 + R wave in aVL >24 mV in men and >20 mV in women
Bundle branch block	Same as pediatric
Right axis deviation	>90 degrees
Left axis deviation	>−30 degrees
Intraventricular conduction delay	Same as pediatric
Nonspecific ST-T changes	Same as pediatric
Strain	Same as pediatric

Table 3

Summary of Electrocardiogram Findings (n = 239)

Electrocardiogram Finding	n (% of subjects)
Nonspecific ST-T changes	127 (53%)
Right axis deviation	77 (32%)
Left ventricular hypertrophy	46 (19%)
LVH with strain	38 (16%)
Right ventricular hypertrophy	30 (13%)
RVH with strain	12 (5%)
Left atrial enlargement	21 (9%)
Right atrial enlargement	15 (6%)
Right bundle branch block	15 (6%)
Left axis deviation	9 (4%)
Biventricular hypertrophy (LVH+RVH)	8 (3%)
Left bundle branch block	3 (1%)
Abnormal PR interval	3 (1%)
Short PR	1 (<1%)
Long PR (first degree AV block)	2 (<1%)
Intraventricular conduction delay	1 (<1%)
Prolonged QTc interval	1 (<1%)

Abbreviations: LVH, left ventricular hypertrophy;; RVH, right ventricular hypertrophy

Table 4

Select Electrocardiogram Findings by Age Group

Age	LVH	RVH	LAD	RAD	ST-T Δ
	n (% age group)	n (%)	n (%)	n (%)	n (%)
0–6 y	1 (33%)	0 (0%)	0 (0%)	0 (0%)	2 (67%)
6–12 y	11 (38%)	9 (31%)	2 (7%)	14 (48%)	11 (38%)
12–18 y	15 (19%)	18 (23%)	3 (4%)	28 (36%)	42 (54%)
>18 y	15 (13%)	2 (<1%)	4 (3%)	33 (28%)	58 (49%)

Abbreviations: LAD, left axis deviation; LVH, left ventricular hypertrophy;; RAD, right axis deviation; RVH, right ventricular hypertrophy; ST-T Δ, nonspecific ST-T wave changes.

Table 5

Multivariate Logistic Regression Analysis of Electrocardiogram Findings Using Age, Sex, and GAA Repeat Length

	LVH	RVH	LAD	RAD	ST-T Δ	Normal ECG
Age	$P = .026^*$	$P = .001^*$	$P = .217$	$P = .013^*$	$P = .837$	$P = .295$
Sex	$P = .006^*$	$P < .001^*$	$P = .042^*$	$P = .482$	$P = .401$	$P = .004^*$
GAA	$P = .668$	$P = .042^*$	$P = .523$	$P = .093$	$P = .039$	$P = .003^*$
Overall *P* Value	$P = .002^*$	$P < .001^*$	$P = .008^*$	$P < .001^*$	$P = .062$	$P < .001^*$
R^2	.09	.39	.20	.08	.03	.28

*Denotes significance

Abbreviations: ECG, electrocardiogram; GAA, shorter triplet GAA repeat length; LAD, left axis deviation; LVH, left ventricular hypertrophy;; R^2, R^2 for overall model; RAD, right axis deviation; RVH, right ventricular hypertrophy;; ST-T Δ, nonspecific ST-T wave changes.