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Cardiomyopathy in Patients with Friedreich's Ataxia – Appearance and Diagnostic Value

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Among the heredoataxias which appear partially similar, Friedreich's ataxia (FA) attracts attention because of concomitant hypertrophic cardiomyopathy (HCM) which decreases life expectancy of FA patients explicitly despite moderate clinical symptoms. Single cases of sudden cardiac death are described. This prospective study faces the appearance of HCM in FA-patients including rhythmologic features and its diagnostic value in separating FA and non-Friedreich heredoatactic patients (NFA).

22 FA patients, 28 non-Friedreich heredoatactic patients and 22 healthy controls were compared using their history, 12-channel electrocardiograms (ECG), Holter monitoring, signal-averaged electrocardiograms as well as their echocardiographic results.

Dyspnoea and chest pain were present in nearly every third FA patient, hardly in NFA patients. Abnormalities according to ECG were far more significant in the FA group with a proportion of 86 % (19 of 22) abnormal ECGs in contrast to both other groups. Almost all abnormal ECGs of FA patients revealed typically ST-T inversions in the inferior limb and lateral precordial leads. Regarding all three groups ventricular late potentials in signal-averaged electrocardiograms occured with normal incidence.

Echocardiography offered strict differences in mean left ventricular wall thickness (p < 0.0001) – FA group with 11.3 mm against the NFA group with 9.1 mm and control group with 8.7 mm. 64 % of the FA patients and no one from the other study groups presented concentric non-obstructive HCM.

Standard ECG and echocardiography seem to be sufficient methods to differentiate Friedreich's ataxia from other heredoataxias phenotypically, in two out of three FA patients concentric HCM could be proven by heart ultrasonography. Meanwhile ventricular late potentials as a sign of extended danger of ventricular arrhythmia appear in normal frequencies. *J Clin Basic Cardiol 2000; 3: 167–71.*

Key words: Friedreich's disease, hypertrophic cardiomyopathy

In the course of a neurodegenerative process inherited ataxias show increasing impairment of gait and stance. The phenotypic appearance of the different inherited ataxias is quite similar and, as a consequence, a definite clinical diagnosis is difficult, especially since disorders of this kind are rare. Nevertheless, patients with Friedreich's ataxia (FA), the most frequent inherited ataxia, suffer from hypertrophic cardiomyopathy in contrast to non-Friedreich's heredoataxias (NFA).

As early as 1863, Nikolaus Friedreich described cardiac symptoms in patients suffering from that autosomal recessively inheritable neurodegenerative disorder supplied with his name [1]. Generally, Friedreich's disease begins between the 8th and 13th year of life [2–4] at a prevalence of 1 to 2 per 100,000 [5–7], and most Friedreich's ataxia patients become wheelchair-bound before they are 20 years old. Progressive ataxia of gait and limbs, dysarthria as well as decrease in position and vibration sense in lower limbs are results of increasing spinocerebellar degeneration caused by a defect that is located on chromosome 9 [8].

Significance of cardiac involvement in Friedreich's disease on the one hand consists in the diagnostic differentiation between heredoataxias. But diagnosis of the most frequent non-Friedreich's heredoataxias can be confirmed genetically today as in the case of Friedreich's disease [9, 10]. However, clinical and prognostic meaning of hypertrophic cardiomyopathy in patients with Friedreich's disease is far more important, since mean life expectancy between 27 and 38 years [8, 11–13] is mostly determined not by central nervous degeneration but by concomitant cardiac disease. Among 82 dead FA patients Hewer [13] described 56 % that died by congestive heart failure, 17 % died by pulmonary or embolic complications. There were in total 75 % of Hewer's observed cases that showed congestive heart failure. Atrial fibrillation or flutter is described in up to 30 % of examined FA groups. Sudden cardiac death is mentioned in FA patients, some of whom had rare or even no cardiac symptoms before [12, 14], but where autopsy revealed hypertrophic hearts. In connection with ventricular tachycardia one case of sudden cardiac death showed ventricular late potentials [15] maybe as electrophysiological correlate of altered heart muscle tissue. Such late potentials might suggest increased danger of ventricular arrhythmia.

The non-Friedreich's ataxias – cerebellar, olivo-ponto-cerebellar ataxias and spastic paraplegia should be mentioned here – do not show cardiac features. Generally they are not as well known and occur together nearly as frequently as Friedreich's disease [16].

This presentation demonstrates the results of our prospective study based on the results taken by three study groups. In consideration of the heart muscle disease decreasing life expectancy, this paper shows comparisons between patients with Friedreich's disease on the one hand and patients with non-Friedreich's heredoataxias as well as healthy controls concerning clinical, electrocardiographic and echocardiographic findings. This is carried out in order to find the appearance of this concomitant cardiac disease and to ascertain the frequency of association between Friedreich's ataxia and disorder of the heart. In the light of previously described Friedreich-atactics with sudden cardiac death we performed Holter monitoring and high-amplified signal-averaged electrocardiograms (SAE) to register ventricular late potentials.

Methods

Classification of groups

The division of the two heredoatactic groups was carried out at the Department of Neurology in St. Josef-Hospital, Ruhr-University of Bochum. The non-Friedreich-heredoatactic group consisted of patients with a secure diagnosis of a hereditary ataxia. Diagnosis and differentiation of these heredo-ataxias (by clinical picture, nerval conduction measurements, magnetic resonance tomography) are complex but possible, even if all these disorders include an increasing disability to walk or to stand. Especially Friedreich's ataxia followed phenotypical criteria by the "Quebec Cooperative Study of Friedreich's Ataxia" [17] with a modification by Harding [3]:

1. Beginning of the disease after the 20th year of life (according to Harding after the 25th year of life)
2. Ataxia of the lower limbs
3. Progression of the ataxia without remission over the last two years
4. Dysarthria
5. Reduction of vibration sensing in the lower limbs
6. Muscle weakness
7. Loss of the deep tendon reflexes of the lower limbs

Healthy candidates were included in this study if prequestioning offered no cardiac and neurologic disorders nor cardiac and neurological heredopathias of relatives.

Registration of data

Basic data, anamnesis and clinical picture
Apart from basic data (height, weight, body mass index, age) particularly cardiac symptoms and risk factors were noted as well as chronological data and neurologic impairment of heredoatactic patients. Every patient's history was recorded according to a standardized questioning protocol.

ECG, Holter monitoring, signal averaged ECG (SAE)
The duration of PQ, QRS, QT intervals and P waves were read using standard twelve channel electrocardiograms at rest. Sokolow-Lyon-index, electric heart axis, R/S-change, number of Q waves and alignment of ST segment and T wave were also recorded.

Holter monitoring delivered maximal, minimal and mean heart rates as well as arrhythmia of the heart in the form of atrial ventricular events and also registered according to LOWN classification.

Ventricular late potentials could be detected by signal-averaged electrocardiograms (device: Fidelity Medical LP 3000). Table 1 shows the three relevant SAE parameters and their normal values. Since two of these three parameters remain outside of normal ranges – see table 1 – there are ventricular late potentials [18].

Echocardiography
Following parameters obtained by transthoracic two-dimensional, m mode, Doppler and coloured Doppler echocardiography are listed in table 2.

Table 1. Signal-averaged electrocardiogram (SAE)

SAE-parameter	Normal range
LAS 40	< 38 ms
RMS 40	> 25 mV
QRSD	< 114 ms

LAS 40: duration of micropotentials (in microvolts) in the terminal QRS complex below 40 mV; RMS 40: refers to the mean amplitude of the last 40 milliseconds of the QRS complex; QRSD: duration of the high-amplified signal-averaged QRS complex

The terms "E" and "A" specify the mitral valves haemodynamic – the maximum of early diastolic opening (E) and the maximum of aperture movement caused by atrial contraction (A). Signs of heart valve failure and shunt failure were also recorded.

Statistics

Statistical evaluation has been made by using the U test by Mann and Whitney and also by using the chi-square test.

Results

Basic data, clinical appearance

Between 1993 and 1996 22 patients with Friedreich's disease (FA) and 28 patients suffering from a non-Friedreich's heredo-ataxia (NFA) that were admitted to the Department of Neurology at St. Josef Hospital, Ruhr-University of Bochum, were taken up in this study. They underwent cardiological examinations at the Medical Department of St. Josef Hospital, Ruhr-University of Bochum, just as 22 healthy control persons did.

All NFA-patients were adults, one of the healthy probands was seventeen years old while five Friedreich-atactics were under age at the time of examination, two of twelve, one of thirteen and two of seventeen years of age. Table 3 shows distribution of sex and age.

Concerning body weight and surface of patients with Friedreich's disease there were minor differences ($p < 0.05$) comparing non-Friedreich's atactics and controls.

The dimension of neurological impairment is reproduced by using a three-grade scale in table 4.

Table 2. Echocardiographic parameters

Parameter	Abbreviation
Left ventricular diameter Diastolic/systolic	LVDD/LVDS
Ventricular septal thickness Diastolic/systolic	IVSD/IVSS
Left ventricular free wall Diastolic/systolic	LVPWD/LVPWS
Aortic diameter	Ao
Left atrial diameter	LAD
Maximum velocity:	
– aortic valve	VmaxAo
– mitral valve	VmaxE/A
Velocity-time-index:	
– aortic valve	VTIAo
– mitral valve	VTIE/A
Middiastolic backmove of anterior mitral valve	EF-Slope

Table 3. Distribution of age and sex

	n	Mean age (years)	Range (years)	Male	Female
Friedreich's ataxia	22	27.3	12–46	64 %	36 %
Non-Friedreich's ataxia	28	42.2	23–63	29 %	71 %
Healthy controls	22	25.5	17–40	23 %	77 %

Table 4. Mobilization

	FA patients (n = 22)	Non-FA patients (n = 28)
No essential handicap	18 %	67 %
Walking aid required	18 %	29 %
Wheelchair-bound	64 %	4 %

Physical handicap of the Friedreich's atactics is noticeably more severe than the NFA group – 64 % of the FA and 4 % of the NFA patients are wheelchair bound.

Referring to cardiac signs three to four cases of all heredoatactics complained about general weariness differing strictly from the control persons. Nearly every fourth FA candidate mentioned palpitations contrary to one out of 23 NFA patients and none of the control persons. A significant distinction consists in the occurrence of dyspnoea and chest pain among Friedreich's heredoatactics. Every third FA patient (n = 22) complained about dyspnoea – three even at rest – or chest pain – two of them at rest – while just two of the NFA patients (n = 28) suffered from dyspnoea at exercise. None of the non-Friedreich's patients nor the controls complained of chest pain.

Cardiac risk factors (smoking, arterial hypertension, diabetes mellitus) show no basic difference between the three observed groups.

Standard electrocardiogram (ECG), Holter monitoring, Signal-averaged ECG (SAE)

Concerning heart axis and heart rhythm – a sinus rhythm in all groups – the comparison of standard ECGs shows similar results. There is one control person with an incomplete right bundle-branch block. Comparing heart rates with 82 beats per minute among Friedreich's atactics and 80 beats per minute among non-Friedreich's heredoatactics the mean heart rate of the control group is lower with 65 beats per minute. Mean duration of P waves, QRS complex, PQ and QT interval are higher in the non-Friedreich's and the control group than in the Friedreich's patients. Particularly the PQ duration of 133 ms is distinctly lower in the FA group (p < 0.01).

High Sokolow-Lyon index, Lewis index and left axis deviation do not occur preferably in any one of the three groups. Two electrocardiograms of Friedreich-atactic patients indicate left ventricular hypertrophy – one with left axis deviation, one with a Sokolow-Lyon index of 3.9 millivolts. Likewise, two standard ECGs of NFA patients (in each case one positive Sokolow-Lyon index and one positive Lewis index) and even one ECG of a control person otherwise not having cardiac abnormalities (but high Sokolow-Lyon index) demonstrate left-ventricular hypertrophic signs.

However, repolarisation abnormalities provide an explicit difference between Friedreich's patients and the other two groups. Comparing the ST-segment alignments referring to the isoelectric line there is a ST segment lowering in nearly every second electrocardiogram of FA patients (10 of 22 persons) contrary to two NFA patients (appraising 19 ECGs in this group). Regarding limb and precordial leads only three FA patients (14 %) and none out of the two other groups have ST segment elevations.

T wave inversions – typically affecting lead III, aVF and most significantly leads V5–V6 – occurred in 17 of 22 Friedreich's patients (78 %). Figure 1 demonstrates this characteristic electrocardiographic finding for the three study groups.

Altogether 19 of the 22 patients (86 %) with Friedreich's disease have abnormal electrocardiograms in contrast to 3 ECGs out of 19 non-Friedreich's heredoatactic cases and one healthy control person with a single positive Sokolow-Lyon index.

Holter monitoring, which was available from 16 FA-patients, 12 NFA-patients patients and 17 control persons, offered a comparatively higher mean heart rate among Friedreich's patients than in the other groups (93 bpm versus 87 bpm in NFA-patients and 81 bpm in control persons). While atrial fibrillation or flutter could not be detected one FA patient and two NFA patients had a few supraventricular extra-systoles. Ventricular arrhythmia could be detected in four cases of FA – three times LOWN type I and one time LOWN type III – and in five cases of NFA – three times LOWN type I and two times LOWN type II. The LOWN type III is present in a seventeen-year old FA patient with slightly thickened left ventricular walls (IVSD 12 mm, LVPWD 11 mm) having several couplets.

Ventricular late potentials diagnosed in accordance with the criteria of Breithardt et al. [18] are obtained in two cases out of each group. High-resolution signal-averaged electrocardiograms (SAE) were available from 22 persons out of the FA and the control group as well as from 23 NFA-patients. So the proportion of ventricular late potentials in each group does not exceed the ten-percent mark.

Echocardiography

Echocardiographic measurements do not reveal essential dissimilarities concerning aortic diameter, left atrial diameter, EF slope or fractional shortening which ranged between mean values of 42 % (FA group), 40.5 % (NFA group) and 37 % (healthy controls).

Mean left ventricular systolic and diastolic diameters of the three investigated groups separated merely according to the absolute values. Referring to the body-surface weighted values – five Friedreich's patients were under age – there is no significant difference; except that four of the 28 non-Friedreich's patients have left ventricular end-diastolic diameters larger than 56 mm. Table 5 shows the mean left ventricular dimensions.

Absolute measurements of left ventricular wall thickness (see table 5) as well as body-surface weighted values differed clearly between patients with Friedreich's disease on the one hand and patients with non-Friedreich's heredoataxia and healthy controls on the other hand. The mean values of the half sums of both left ventricular walls in the end-diastole – therefore for each group the mean value of half amount of end-
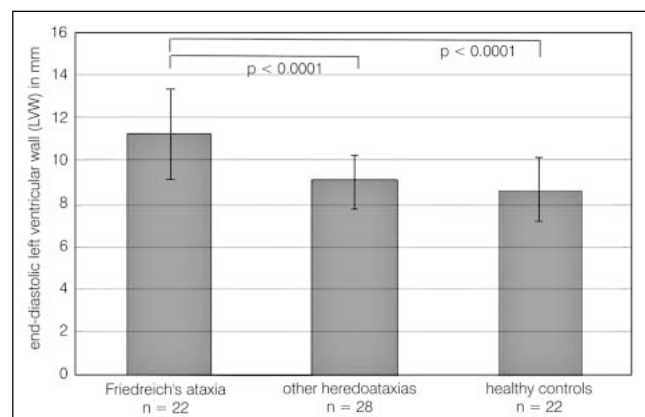
Figure 1. Mean left ventricular wall thicknesses of hearts measured by transthoracic echocardiography show obviously higher values among patients with Friedreich's ataxia compared to non-Friedreich's ataxia patients and control persons

Table 5. Echocardiographic left ventricular dimensions

|	FA patients (n = 22)		NFA patients (n = 28)		Healthy Controls (n = 22)	
	Mean	Median	Mean	Median	Mean	Median
LVDD (mm)	41.3	40	46.8	46.5	47.2	50.1
LVDS (mm)	24.1	23.5	29.6	29	27.9	29
IVSD (mm)	11.3	11	9.1	9	8.7	8.8
IVSS (mm)	16	16	14.7	14.5	14.3	14.7
LVPWD (mm)	11.3	11	9.1	9	8.7	8.8
LVPWS (mm)	16.7	16	14.3	14	15.1	15

diastolic free-wall (LVPWD) and ventricular septal thickness (IVSD) – differs strictly between the examined groups as well (see figure 2).

The mean end-diastolic wall thickness of the left ventricle among the Friedreich's patients is 11.3 mm (range 8.0 to 15.0 mm), compared to 9.1 mm in the NFA group (range 6.0 to 11.5 mm) and 8.7 mm in the control group (range 6.0 to 11.4 mm). 12 out of 22 FA patients have left ventricular wall thickenings equal to or greater than 12.0 mm. Furthermore two children – a 14-year old girl with 10.5 mm and a 15-year old boy with 11.0 mm – have left ventricular walls above their age-matched normal ranges [19]. None of the non-Friedreich's heredoatactics nor the control persons offered thickened heart walls. The results of the body-surface weighted values for the mean left ventricular wall (LVW/body surface) are 6.7 mm/m^2 in the FA group, 5.0 mm/m^2 in the NFA collective and 4.7 mm/m^2 among control persons.

The left ventricular wall ratio (IVSD/LVPWD) amounts to a little bit more than 1.0 in six of the 22 Friedreich's patients, but not one of all the study participants had a ratio higher than 1.3 which would be an indicator of asymmetrical septal hypertrophy (ASH).

All in all, there is no person among the non-Friedreich's heredoatactics nor in the control group presenting left ventricular hypertrophy whereas 14 of 22 patients (64 %) with Friedreich's ataxia have left ventricular hypertrophy compatible with a concentric hypertrophic cardiomyopathy.

Doppler echocardiographic examination does not uncover basically diverse results applying to maximum speed and velocity-time index above aortic and mitral valves. There was no evidence of shunt or heart valve failure shown in the results of Doppler or coloured Doppler ultrasonography.
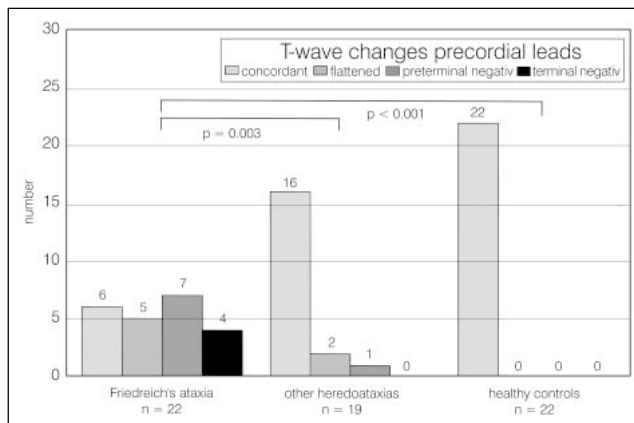
Figure 2. Standard electrocardiograms of patients with Friedreich's disease provide negative alignment of T waves deviating significantly from non-Friedreich heredoatacics and healthy controls

Table 6. Cardiological findings in other studies

	n	Abnormal standard ECG	Hypertrophic cardiomyopathy
Alboliras [23]	22	82 %	68 %
Andermann [30]	32	75 %	
Boyer [31]	33	52 %	
De Michele [32]	36	72 %	
Giunta [22]	50	80 %	34 %
Gottdiener [26]	25	52 %	56 %
Grenadier [24]	20		70 %
Harding [29]	114	75 %	
Own results	22	86 %	64 %

Discussion

This study presents concentric left ventricular hypertrophy among 14 of 22 examined patients suffering from Friedreich's disease (64 %). According to other patho-histological [13, 20, 21] and clinico-instrumental examinations these 14 heredo-atactic patients have a concomitant hyper-trophic non-obstructive cardiomyopathy. Giunta [22] found 17 of 50 examined patients with Friedreich's disease (34 %) that revealed hypertrophic cardiomyopathy; smaller studies ascertained shares of 68 % [23] and 70 % [24]. Some authors describe sporadically appearing asymmetric septal hypertrophy [22–24] although seldom connected with left ventricular outflow obstruction[13, 25]. Also rarely documented dilative cardiomyopathies in Friedreich-patients [22, 23, 26] are considered as a progression of hypertrophic forms [27, 28].

Abnormal standard 12-channel electrocardiograms, nearly always linked with typical T inversions in leads I, aVF and V$_4$ to V$_6$, are present in 19 of 22 available ECGs of this Friedreich group (86 %). Larger observations of Friedreich's disease obtained abnormal ECGs in 80 % in the case of Giunta [22] (n = 50) and in 75 % in the case of Harding [29] (n = 114). Table 6 gives a survey of available studies.

Except for Grenadier [26] other authors found similar dimensions of the left ventricle [22, 23, 33, 34]. The own investigation offers values of 11.3 mm thickness for the ventricular septum and the left ventricular free wall. This corresponds to the results of Alboliras [23] with 11.4 mm (n = 22). But these comparisons are precarious not least since all echocardiographic examinations of FA patients have groups containing no more than 50 persons showing various stages concerning the progression of hypertrophic cardiomyopathy.

Doppler echocardiographgy does not provide essential differences between FA patients and other heredoatactics or healthy controls. These results confirm Giunta's findings [22]. Left ventricular hypertrophy or electrocardiographic abnormalities of non-Friedreich heredoatactics, particularly the T inversions mentioned above, are not recorded [26].

As a clinical indication of concomitant cardiac disease about every third patient with Friedreich's ataxia in this study reports dyspnoea or chest pain. This is significantly more than in non-Friedreich's heredoatactics which may in the case of dyspnoea result from the comparatively far higher grade of immobilisation in FA patients presuming that dyspnoea comes from deficient physical mobility. Other authors found similar frequencies of dyspnoea and chest pain [22, 29].

However, immobilisation might also mask cardiac symptoms and symptomatic appearance seems to be small indeed facing the fact that 91 % (20 out of 22) of the examined FA patients have either pathological 12-channel ECGs or pathological echocardiographic results. This high proportion rather substantiates the assumption of Geoffroy [17], of Therriault [35] in his myocardscintigraphical study and of Hawley [36] in his 5-year-follow-up study that almost every Friedreich's patient develops hypertrophic cardiomyopathy.

Explicit evidence concerning particular danger through cardiac complications or sudden cardiac death, described by Côté [37], Gottdiener [26] and Hewer [11], can not be seen in this examination. There is a case report by Zimmermann [15] pointing out late ventricular potentials connected with Friedeich's ataxia.

Histological appearance of hypertrophic cardiomyopathy in the course of Friedreich's disease is specified by focal myocyte degeneration, focal fibrosis and necrosis [34, 38]. But this alteration of heart tissue seems not to be substrate for generating ventricular late potentials; 9 % (2 of 22) of the examined

FA patients have late potentials. Like the other two study groups this result is in a normal range [39]. This may signify that none of the 22 FA patients has a special danger of ventricular arrhythmia, on the other hand there are cases of Friedreich's ataxia with inconspicuous cardiac examinations that died suddenly [11].

Nevertheless, this suggests that registering of late potentials is not a sufficient instrument to detect increased danger of ventricular arrhythmias in FA patients as opposed to myocardial infarction where there is an increased danger of complex ventricular arrhythmia if late potentials as an electrophysiologic correlate of altered heart tissue occur [40–42].

In two out of three patients with Friedeich's disease hypertrophic non-obstructive cardiomyopathy is verifiable and standard 12-channel-electrocardiography as well as echocardiography are suitable methods in the differential-diagnostic demarcation of heredoataxias. Even if 91 % of the FA patients in this study have pathological cardiological signs (ECG, ultrasonography), there was none of them showing severe arrhythmias nor needing cardiological treatment. But according to Hewer, three of four FA patients die as a direct or indirect consequence of cardiac involvement, so aggravation of cardiac involvement has to be expected in our patients and especially in the case of congestive heart failure, atrial fibrillation, pulmonary complications or complex ventricular arrhythmias it has to be treated. Facing cardiomyopathy distinctly decreasing life expectancy there is a necessity of regular cardiological care of patients with Friedreich's disease, especially since neurologic impairment and immobilisation influence everydays life more than comparatively modest cardiological symptoms.

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