The heart in Friedreich's ataxia

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SUMMARY Seventeen patients with Friedreich's ataxia were investigated for cardiac abnormalities using non-invasive methods. Clinical examination, routine chest radiographs and electrocardiograms were a poor guide to underlying heart involvement but using continuous ambulatory electrocardiographic monitoring, echocardiography and isotope ventriculography all patients were found to have abnormalities, even when the neurological signs were minimal.

Abnormalities of the heart in patients with Friedreich's ataxia have been noted since the original description of the disease.¹ The clinical assessment of the cardiac status is unreliable as symptoms and signs of heart involvement usually occur late in the course of the disease.² Although electrocardiographic studies have shown abnormalities in the majority of patients the changes are varied and non-specific.^{3,4} Recent reports of echocardiographic findings have shown conflicting results.⁵⁻⁷

In an attempt to characterise the cardiac manifestations of Friedreich's ataxia in more detail and to assess the most useful methods of detection we performed a battery of non-invasive tests in seventeen patients. All patients were found to have abnormal cardiac function by one or more of these investigations.

Patients and methods

(A) Patients

Seventeen of the eighteen patients with a diagnosis of Friedreich's ataxia who were known to the medical neurology department of Edinburgh hospitals agreed to participate in the study. Only patients satisfying the diagnostic criteria used by the Quebec Co-operative Study of Friedreich's ataxia were included.⁸ Thus all patients had shown the clinical onset of disease before the age of twenty years; all had progressive ataxia, dysarthria, decrease in proprioceptive sensation, muscle weakness and loss of tendon reflexes. Plantar responses were extensor in sixteen of the seventeen patients, scoliosis was found in all patients and pes cavus in fourteen. The patient's neurological disability was graded on an arbitrary scale from minimal disability with full independence (Grade 1) through to severely disabled with marked dysarthria and ataxia, areflexia and

wheelchair bound (Grade 4). There were ten male and seven female patients with a mean age of 24.5 (range 11 to 43) years. The mean duration of illness was 13.6 (range 0.5 to 30) years. All were Caucasians. The patients comprised twelve family groups with four affected siblings in one family and three in another. One patient had an affected sibling who was unwilling to participate in the study.

(B) Methods

Each patient had a full clinical cardiological assessment, twelve lead electrocardiogram (ECG), chest radiograph and echocardiogram. Twenty-four hour continuous ambulatory ECG monitoring was done in sixteen patients, radionuclide ventriculography in eleven and autonomic function tests in ten patients.

(1) *ECG and continuous ambulatory ECG monitoring* The criteria used for defining left ventricular hypertrophy conformed to those of the "Minnesota" code.⁹ Ambulatory ECG monitoring was done using a Medilog I Recorder (Oxford Medical Systems Ltd, England) for periods of twenty-four hours. Analysis was undertaken using a Pathfinder High Speed ECG Analyser (Reynolds Medical Ltd, England) with a visual inspection of the recording at sixty times original speed. The analysis was done by a cardiologist experienced in ambulatory ECG interpretation.

(2) *Autonomic function studies* consisted of the heart rate response to the Valsalva manoeuvre, deep breathing and standing up and the blood pressure responses to standing and to sustained handgrip as described in detail previously.¹⁰⁻¹²

(3) *Isotope Ventriculography.* Gated radionuclide ventriculography was performed after the intravenous injection of 15 mCi technetium 99 m electrolytically labelled human serum albumin. Patients were examined at rest in the supine position with the gamma camera (Nuclear Enterprises MkV) positioned to give a 30 degree left anterior oblique projection with a 10 degree caudal tilt. Details of the method have been described previously.¹³ Left ventricular ejection fraction was calculated using the ratio of counts in end-systole (ES) to counts in end diastole (ED):

$$\text{Ejection Fraction (EF)} = \frac{\text{ED} - \text{ES}}{\text{ED} - \text{background correction}}$$

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The background correction was taken from a crescentic shell along the free margin of the left ventricle normalised to an area equal to the left ventricle. The normal control EF values from twelve apparently healthy subjects of similar age ranged from 0.51 to 0.65.

Echocardiograms. A SK1 Ekoline 21 M-mode echocardiogram and a RT400 or an Irex III real time cross sectional recorder were used to determine left ventricular cavity size and wall dimensions, to identify the motion of the mitral valve and to assess left ventricular function. The techniques and measurements were performed as previously described.¹⁴⁻¹⁶ The following measurements were used: LVD = Left ventricular diastolic dimension, LVS = Left ventricular systolic dimension, IVS = Interventricular septal thickness, LVPW = Left ventricular posterior wall thickness, SAM = Systolic anterior motion of the mitral valve, FS = Fractional shortening = $(LVD - LVS)/LVD \times 100$. Real time echocardiographic assessment of left ventricular function was graded 1 = normal, 2 = impaired, 3 = severely impaired.

Results

CLINICAL FEATURES AND CHEST RADIOGRAPH (table 1)

None of the patients had volunteered any cardiac symptoms at the time of presentation but twelve patients admitted to some degree of exertional dyspnoea on direct enquiry and four had palpitations, two dizziness and one chest pain of a paroxysmal nature unrelated to exercise. Two patients had noticed ankle swelling at some stage in their illness. All patients were in sinus rhythm with no signs of cardiac failure at the initial clinical cardiological assessment although one (Patient 10) had

atrial flutter at a subsequent review. Eight patients had soft systolic murmurs of variable intensity either at the apex or at the lower left sternal edge. Cardiac enlargement was not present clinically in any of the patients. Radiological assessment of cardiac size was impossible in eight patients because of the severity of the kyphoscoliosis. Of the other nine only two patients, both of whom had moderate kyphoscoliosis, had cardiothoracic ratios greater than 50%.

ECG AND AMBULATORY ECG MONITORING (table 2)

Routine 12 lead ECGs showed sinus rhythm in all except one patient (Patient 10) who had atrial flutter with 3:1 block. Fourteen of the seventeen patients showed non-specific ST segment changes, T wave inversion or both. The criteria of left ventricular hypertrophy were fulfilled in seven patients. Ambulatory ECG monitoring revealed abnormalities of rhythm in ten patients although all patients were asymptomatic during the recording. Three patients showed abrupt variations in sinus rhythm (Patients 7, 8, 9); two had episodes of supraventricular tachycardia (Patients 12 and 14); two showed atrial fibrillation (Patients 10 and 13); one patient showed frequent runs of ventricular ectopics with up to 5 ectopics sequentially (Patient 3). Episodes of sinus arrest occurred in three patients (Patients 5, 10 and 17). Combining the results of routine and ambulatory ECG records only two patients had normal findings (Patient 2 and 6).

Table 1 Clinical and chest radiograph findings

Patient	Age (yr) and Sex	Neurological Status	Cardiac symptoms	Cardiac murmur	Chest radiograph	
					Scoliosis	Cardiothoracic ratio
1	11 F	3	Slight ED	2/6 systolic	Marked	Not measurable
2	13 M	4	None	None	Slight	93/249
3	14 F	4	Slight ED	2/6 systolic	Marked	Not measurable
4*	14 F	1	Slight ED	3/6 systolic	Slight	100/218
5	16 M	2	Slight ED	None	Slight	105/250
6	17 M	2	None	None	Marked	Not measurable
7*	20 M	2	None	None	Slight	118/254
8*	21 M	2	Slight ED	None	Slight	122/288
9*	22 M	2	Moderate ED	2/6 systolic	Slight	127/275
10	26 M	4	Palpitations	None	Moderate	155/277
11	28 F	3	Marked ED	2/6 systolic	Slight	122/254
12	31 F	3	None	None	Marked	Not measurable
13†	32 M	4	Palpitations	None	Marked	Not measurable
14†	34 M	4	Dizziness on exertion	2/6 systolic	Marked	Not measurable
15	36 F	4	Moderate ED	None	Marked	Not measurable
16†	39 F	4	Moderate ED	3/6 systolic	Marked	Not measurable
17	43 M	4	Marked ED	None	Marked	Not measurable
			Orthopnoea			
			Palpitations			
			Moderate ED			
			Moderate ED			

* and † = different family groups
ED = Exertional Dyspnoea

Table 2 12 lead and 24 hour ambulatory electrocardiogram and radionuclide ventriculogram results

12 Lead ECG				Ambulatory monitor		Radionuclide ventriculogram	
Patient	Rhythm	ST/T Wave changes	Left ventricular hypertrophy	Rhythm	Sinus arrest	Ejection fraction	Wall movement
1	Sinus	ST changes	Present	No Recording	No Recording	No Recording	No Recording
2	Sinus	None	None	Sinus	None	No Recording	No Recording
3	Sinus	ST changes	None	Sinus with ventricular tachycardia	None	No Recording	No Recording
4*	Sinus	ST changes	Present	Sinus	None	0.69	Impaired
5	Sinus	T wave inversion	None	Sinus with abrupt sinus node variation	Present	0.50	Impaired
6	Sinus	T wave inversion	None	Sinus	None	0.56	Normal
7*	Sinus	Right axis deviation	Present	Sinus with sinus node variation	None	0.62	Normal
8*	Sinus	ST changes	Present	Sinus with abrupt sinus node variation	None	0.77	Normal
9*	Sinus	ST changes	Present	Sinus with abrupt sinus node variation	None	0.79	Normal
10	Atrial flutter with 3:1 block	ST changes	None	Sinus with paroxysmal atrial fibrillation	Present (>2 s delay)	0.32	Impaired
11	Sinus	ST changes	Present	Sinus	None	0.60	Normal
12	Sinus	ST changes	None	Sinus with supra-ventricular tachycardia	None	0.62	Normal
13†	Sinus	T wave inversion	None	Atrial flutter fibrillation	None	No Recording	No Recording
14†	Sinus	T wave inversion	None	Sinus with supra-ventricular tachycardia	None	0.64	Normal
15	Sinus	ST changes	Present	Sinus	None	0.61	Normal
16†	Sinus	ST changes	None	Sinus	None	0.59	Normal
17	Sinus	T wave inversion	None	Sinus	Present	No Recording	No Recording

AUTONOMIC FUNCTION STUDIES

Autonomic function studies were done in ten of the seventeen patients. The studies were limited because of the patient's motor disability which meant that tests could not be performed in the most severely affected patients. No significant abnormalities were found.

ISOTOPE VENTRICULOGRAPHY (table 2)

Radionuclide ventriculograms were performed in eleven patients. Reduced ventricular function was found in only two patients (Patients 5 and 10) both of whom showed regional areas of hypokinesis. In patient 5 the EF was 0.50, only just below that of the control group (range 0.51 to 0.65) while in patient 10 it was much reduced at 0.32. In contrast to these two patients the most striking finding was the apparently very vigorous contraction in all other patients studied. The ventricular appearances in the left anterior oblique projection showed a long thin ventricle with wide separation between the two ventricles suggesting ventricular hypertrophy. Left ventricular EF for these patients was in the high, normal region and in three siblings (Patients 4, 8 and 9) it was in excess of 0.69.

ECHOCARDIOGRAPHY (table 3)

Left ventricular wall thickness was increased in

fifteen of the seventeen patients and the interventricular septum was thickened in thirteen patients. Five patients showed a ratio of septal to posterior wall thickness of 1.3:1 and only two patients (Patients 5 and 10) showed systolic anterior motion of the mitral valve. The fractional shortening was reduced in twelve of the seventeen patients indicating impaired left ventricular functioning. All patients showed an abnormality in at least one of these three measurements.

Discussion

Although cardiac abnormalities were noted at necropsy in three of Friedreich's original six patients¹ he considered the disease a purely neurological one.¹⁷ In a retrospective study of eighty-two fatal cases of Friedreich's ataxia Hewer reported death from heart failure in 46 patients and evidence of cardiac dysfunction during life in 60 patients.¹⁸ The majority of these patients developed cardiac failure only during the last six months of their lives and apart from failure the only other relatively common feature was chest pain.¹⁸ In the largest reported study of the clinical features of the disease Harding described cardiac symptoms in 46 of her 115 patients.¹⁹ Only one of her patients had signs of heart failure and the only common symptom described was, as in our patients,

Table 3 Echocardiographic findings

Patient	LVD (cm)	FS	IVS (cm)	LVPW (cm)	IVS/LVPW	SAM	Real time
1	2.4	29	1.6	1.6	1.3	—	No Recording
2	2.8	14	1.0	1.3	0.7	—	No Recording
3	2.8	21	1.7	1.3	1.3	—	No Recording
4*	3.6	47	1.6	1.5	1.1	—	1
5	3.4	41	1.2	1.5	0.8	—	1
6	4.7	32	1.8	1.8	1.0	—	1
7*	4.0	25	1.5	1.3	1.1	—	1
8*	3.8	42	1.7	1.8	0.9	—	1
9*	3.8	37	2.0	1.5	1.3	+	1
10	5.0	20	1.1	1.3	0.9	—	3
11	3.9	41	1.7	1.3	1.3	+	1
12	4.2	23	1.2	1.2	1.0	—	3
13†	4.8	17	1.1	1.2	0.9	—	2
14†	4.8	23	1.0	1.1	0.9	—	3
15	3.8	24	1.7	1.3	1.3	—	3
16†	3.1	19	1.4	1.5	1.0	—	2
17	4.0	30	1.0	0.9	1.1	—	3
Normal	3.5—5.7	3.4—4.4	0.6—1.1	0.6—1.1	<1.3		

exertional dyspnoea.¹⁹ Other authors have emphasised the difficulty in attributing dyspnoea as a manifestation of cardiac involvement in these patients with their neurological disability.^{2,6,17,20} Symptoms such as chest pain, palpitations and dizziness occur in the minority of patients and many patients with other evidence of cardiac involvement have no symptoms referable to the cardiovascular system.^{6,21} The presence of kyphoscoliosis in the majority of patients severely limits the value of radiography in assessment of heart size although it has been suggested that heart size may increase in the terminal stages of the disorder so that serial radiographs may be of value.²¹

Our finding of non-specific and variable ST segment and T wave changes in fourteen of our seventeen patients on routine 12 lead ECG is similar to the experience of others.^{3,4,18,22} We are not aware of any other published reports of ambulatory ECG monitoring in patients with Friedreich's ataxia. Three of our patients had a history of palpitations (Patients 9, 12, 15) but all patients were asymptomatic during the recording. Supraventricular and ventricular tachycardias have been found in up to 10% of middle-aged apparently healthy subjects and premature beats in less than 5% of young adults.²³ The significance of short episodes of sinus arrest is also unclear. Therefore, although the use of ambulatory ECG monitoring in sixteen of our patients increased the detection rate of arrhythmias over that found with standard ECG no abnormality was particularly prominent and the significance of the abnormalities is not clear.

Several reports of echocardiographic studies in Friedreich's ataxia have suggested that the heart involvement is hypertrophic cardiomyopathy.^{5,6,24} In our group of patients interventricular septal thickness was increased in 65% of patients and left ven-

tricular wall thickness increased in 82%. However, only 29% showed an IVS/LVPW ratio of 1.3 suggestive of asymmetrical septal hypertrophy. Others have reported increased septal thickness in from 36 to 100%; increased left ventricular wall thickness in from 0 to 100% and asymmetric septal hypertrophy in from 0 to 36%.^{5,6,7,24} These variations suggest that there are a range of abnormalities with a concentric thickening of the left ventricle more common than asymmetric septal hypertrophy. This corresponds with the most recent report of the Quebec study.²⁵ To our knowledge there have been no other studies using gated blood pool scanning in Friedreich's ataxia patients. This technique is a useful atraumatic method of evaluation of hypertrophic cardiomyopathy,²⁶ and it was included in our protocol because of the reported high incidence of hypertrophic cardiomyopathy in Friedreich's ataxia. Of the twelve patients who had radionuclide ventriculograms, patients 9, 11 and 15 had echocardiographic evidence of asymmetric septal hypertrophy. None of these patients had a reduced ejection fraction. The three siblings with the abnormally high ejection fractions (Patients 4, 8 and 9) all showed left ventricular hypertrophy on ECG.

The estimated prevalence of Friedreich's ataxia in Sweden is 1 per 100,000 of the population.²⁷ If this applies to Scotland a total number of eighteen cases would be appropriate to the population served by the neurological services in Edinburgh. The Quebec Co-operative Study of Friedreich's ataxia, whose diagnostic criteria we have observed, have reported cardiac involvement in over 90% of patients with eventual involvement in all cases.⁸ Cardiological involvement has been a universal finding in reported necropsy cases of Friedreich's ataxia from American and English literature.²⁷ All of our patients showed some disturbance of cardiac function on one or more

of the investigations done. This would tend to support the hypothesis that the association of heart disease with the neurological features of Friedreich's ataxia is due to the effects of a single pleiotropic gene.^{6,19} Rather than a single cardiomyopathy there appears to be a spectrum of heart involvement with a minority of patients showing an asymmetric septal hypertrophy, the majority showing concentric hypertrophy. There was no clear correlation of type of heart involvement with the neurological disability or with the age of the patient.

Prospective serial cardiac assessment of patients with Friedreich's ataxia especially with echocardiograms and gated blood pool ventriculograms would appear to be a promising method for determining whether there are distinct cardiomyopathies or a progression from the hypertrophic to concentric form as Barbeau has suggested.²⁵ If there are similarities between the heart involvement in Friedreich's ataxia and other cardiomyopathies the study of the evolution of the cardiomyopathy in this disease may well act as a useful model. As the clinical features of cardiac involvement are a poor guide to the cardiac status of patients with Friedreich's ataxia it would appear wise to undertake echocardiograms at least in all patients as a guide to the patient's management.

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