Cardiomyopathy and the electrocardiogram in Friedreich's ataxia

Introduction

Friedreich's ataxia is the most common human hereditary ataxia. Inherited in an autosomal recessive pattern, the symptoms relate to progressive damage to the cerebellum, spinal cord and peripheral nervous system. Patients also frequently develop diabetes and are prone to a cardiomyopathy.

The cause is inadequate production of frataxin, a mitochondrial and cytosolic iron-binding protein. When deficient, multiple iron-sulphur binding proteins lack proper assembly, one consequence of which is mitochondrial iron overload. Proteins, including mitochondrial aconitase and complexes I, II and III of the electron transport chain (Rötig et al, 1997), are impaired, with reduced mitochondrial production of ATP (Lodi et al, 1999). The net effect is mitochondrial and nuclear damage with resultant cell death.

Discussion

Friedreich's ataxia commonly causes hypertrophic cardiomyopathy, which may later transform into a dilated cardiomyopathy. Heart failure is a primary cause of early death in this disease. Patients suffer arrhythmias (often atrial fibrillation) and electrocardiographic abnormalities are seen in over 85% of cases (Alboliras et al, 1986; Child et al, 1986; Schadt et al, 2010). A consistent theme in Friedreich's ataxia is variation in both the cardiomyopathy and the electrocardiogram, and in their interrelationship (Alboliras et al, 1986; Dutka et al, 1999). Alboliras et al (1986) described 15 patients with concentric left ventricular hypertrophy, only three of whom (20%) satisfied electrical voltage criteria for ventricular hypertrophy. Despite more than 90% of electrocardiograms being abnormal, electrocardiographic left ventricular hypertrophy is described in a minority (1–19%) of subjects (Harding and Hewer, 1983; Child et al, 1986; Schadt et al, 2012). Widespread ST segment and T wave inversion are the commonest abnormalities with no authors reporting low QRS voltage (Harding and Hewer, 1983; Child et al, 1986; Schadt et al, 2012).

On a cellular level, the 'hypertrophy' in Friedreich's ataxia is biochemically distinct from that of hypertrophic obstructive cardiomyopathy. In some cases of Friedreich's ataxia the electrocardiogram may show Q waves in the absence of prior myocardial infarction. These appearances, in conjunction with low voltage and increased myocardial wall thickness, are reminiscent of amyloid cardiomyopathy, in which wall thickening is caused by protein deposition and not myocyte hypertrophy. In Friedreich's ataxia there is increased mitochondrial size, iron overload, mitochondrial and nuclear damage. Histological features include diffuse interstitial fibrosis, myocyte 'hypertrophy' and necrosis (Alboliras et al, 1986; Michael et al, 2006).

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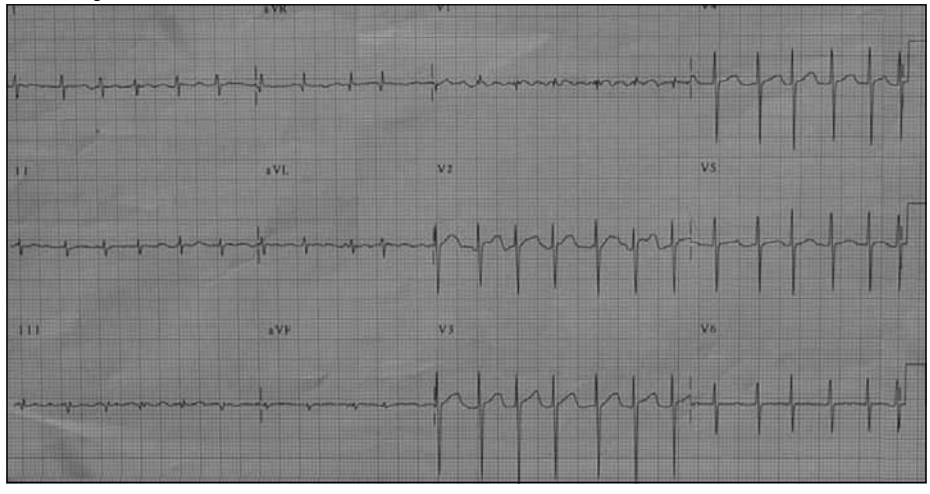
Figure 1. Resting 12-lead electrocardiogram showing atrial fibrillation at 154 beats/min and low limb lead voltage (<0.5 mV in all limb leads).



Case Report

An 18-year-old man presented with a fast irregular pulse. Friedreich's ataxia had been diagnosed when he was 8 years old. At 16 years of age he had undergone surgery for scoliosis. The patient was taking vitamin supplements, omega-3 and cod liver oil tablets. On examination, he was of normal build (body mass index 22.4 kg/m^2), wheelchair-bound, comfortable and apyrexial, with an irregular pulse in excess of 150/min and normotensive at 120/75 mmHg. Oxygen saturations were 97% on room air. Neurological features were compatible with the diagnosis of Friedreich's ataxia.

Blood tests revealed a normal full blood count (haemoglobin 16.2 g/dl), electrolytes, magnesium, calcium, thyroid function (thyroxine 18.6 pmol/litre, thyroid-stimulating hormone 1.26 mu/litre) and mildly elevated C-reactive protein (15 mg/litre). An electrocardiogram showed rapid atrial fibrillation with low voltage morphology (*Figure 1*). The echocardiogram demonstrated concentric left ventricular hypertrophy (*Figure 2*) with normal biventricular systolic function. Long axis (mitral and tricuspid annular excursion) impairment was indicative of diastolic dysfunction.

Treatment was initiated with intravenous metoprolol which was subsequently converted to oral sotalol (80 mg twice daily), digoxin (125 μg daily) and aspirin (75 mg daily) with a view to immediate rate control and potentially chemical cardioversion.

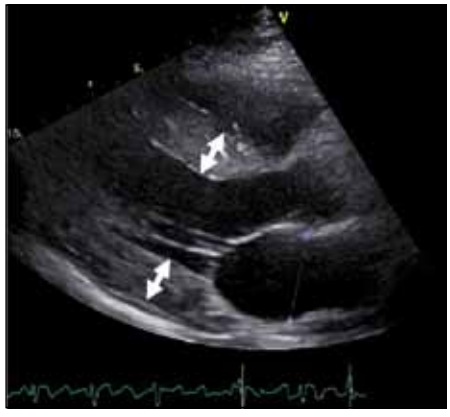


Figure 2. Transthoracic echocardiogram showing a parasternal long axis view with left ventricular hypertrophy (arrows), 1.7 cm in diastole. Ejection fraction 55% and left atrial diameter 3.4 cm.

Santos et al (2010) review the molecular mechanisms causing Friedreich's ataxia.

The net result is a chronic reactive myocarditis with loss of contractile fibres, as opposed to over-expression of contractile fibres as seen in hypertrophic obstructive cardiomyopathy. Coupled with impaired mitochondrial ATP production, this may account for the low voltage electrocardiogram and discrepancies with apparent left ventricular 'hypertrophy' in patients with Friedreich's ataxia.

In terms of presentation this patient, with hypertrophy and an arrhythmia, is not atypical. However, the presence of low voltage in the context of left ventricular hypertrophy on echo, appears unusual. BJHM

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LEARNING POINTS

- Friedreich's ataxia is caused by a deficiency of the iron-binding protein frataxin, which results in mitochondrial and nuclear dysfunction.
- The clinical consequences include spino-cerebellar degeneration, diabetes and cardiomyopathy.
- The cardiomyopathy is usually hypertrophic with heart failure a common cause of early death.
- In a proportion of patients cardiomyopathy develops into a dilated cardiomyopathy status with poor systolic function.
- There is currently no cure for Friedreich's ataxia.

Pacemaker in the wrong pocket

This elderly woman (*Figure 1*) informed her daughter that her 'hearing aid' was broken and for weeks she had kept it safe in her trouser pocket. The hearing aid was in fact her VVIR (ventricular sensing, ventricular pacing, inhibited, rate responsive) pacemaker, which had been implanted 6 years previously for complete heart block. The patient was well and haemodynamically stable.

Remarkably, she had no underlying intrinsic cardiac rhythm and was therefore pacemaker dependent. Fortunately, the system was programmed to pace bipolar; as unipolar pacing only works if the generator box is in contact with subcutaneous tissue. Failure to pace would have been fatal in this case. Although skin erosion is common, complete extrusion is a rare phenomenon. BJHM

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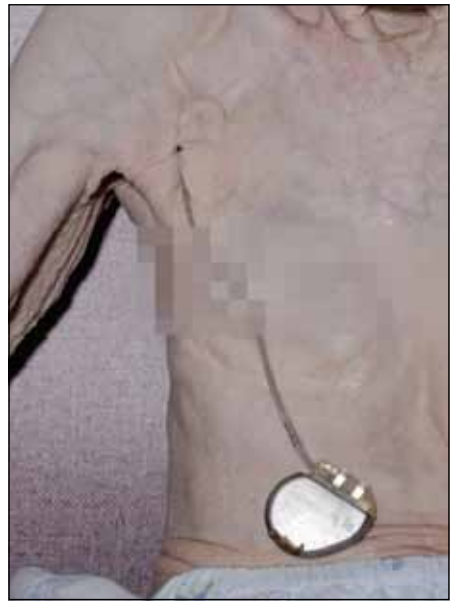

Figure 1. Image showing complete extrusion of the device and wire.