

CASE STUDY

Cardiac involvement in Emery Dreifuss muscular dystrophy: a case series

A E Buckley, J Dean, I R Mahy

Abstract

Three patients with Emery Dreifuss muscular dystrophy are reported. Emery Dreifuss muscular dystrophy is an X linked muscular dystrophy, in which locomotor involvement is characteristically mild and slowly progressive. The effect on the heart becomes apparent in the teenage years and is characterised by cardiac conduction defects and infiltration of the myocardium by fibrous and adipose tissue. It first affects the atria, which results in atrial paralysis; treatment with ventricular pacing is usually needed. Female carriers can develop heart problems and are at risk of sudden death. Relatives of affected patients should be offered screening with electrocardiography and echocardiography.

(Heart 1999;82:105-108)

Keywords: Emery Dreifuss muscular dystrophy; atrial paralysis; sudden death

Emery Dreifuss muscular dystrophy (EDMD) is an uncommon X linked muscular dystrophy. In contrast to the Duchenne and Becker varieties of muscular dystrophy, locomotor abnormalities are mild and progress slowly. Consequently, EDMD is often called a benign form of muscular dystrophy. However, cardiac involvement is a

predominant feature of the disease, and, in young adults, may be the first problem that causes them to present for treatment. This, and the risk of sudden death which affects carriers, as well as patients with locomotor symptoms, increases the importance of this condition to the cardiologist.

We report a family with EDMD which shows the typical features of the associated cardiomyopathy, and review the clinical presentation and underlying pathology linked to this condition. The index case has been reported in the genetic literature,¹ and since the case was first reported, two previously unaffected relatives have developed cardiac involvement.

Case 1

The index case, a 44 year old man, first came to medical attention in 1966, aged 13, when he was admitted to hospital with widespread ichthyosis. During his stay in hospital, he was seen to have flexion deformities of both elbows, plantar flexion deformities of both feet, and a mild degree of kyphoscoliosis. Despite these abnormalities, his mobility was not limited and no unifying diagnosis was made. He had no clinical cardiac abnormalities and no cardiac investigations were done.

The first cardiac abnormality (an irregular pulse) was noted six years later as an incidental finding during hospital admission for treatment of infected eczema. A resting ECG showed an atrial tachycardia with variable atrioventricular conduction. At this time serum creatine kinase activity was raised at 426 U/l (normal < 50 U/l). At this time, the patient was diagnosed with atypical Duchenne muscular dystrophy. During the next five years, the patient was not followed up, and stayed well and free from symptoms.

When he was 24 years old, he presented to the neurology department complaining of decreased mobility and progression of the contractures of the biceps and achilles tendons. Clinical cardiovascular examination revealed a resting bradycardia but no other abnormality. The resting ECG showed atrial standstill with a junctional bradycardia of 37 beats/min (fig 1). Echocardiography showed no abnormality; cardiac chamber dimensions were normal, and myocardial contractility was preserved. Nerve conduction studies were also normal. Once again, no unifying diagnosis was made. In the

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Accepted for publication
25 November 1998

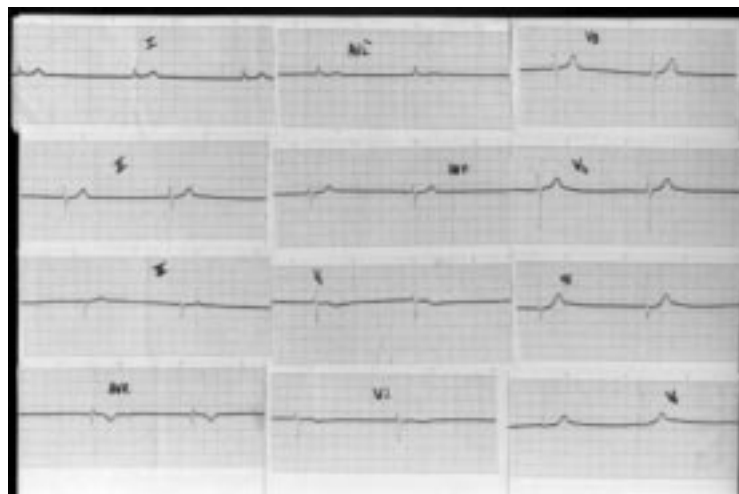


Figure 1 12 lead ECG of case 1 showing a junctional bradycardia of 37 beats/min. P waves are absent.

absence of cardiac symptoms, it was decided to manage him conservatively and he stayed well over the next four years.

In 1982, aged 29, he was admitted for elective surgery to lengthen his achilles tendons. Preoperatively, his resting ECG showed a junctional bradycardia; ambulatory ECG showed episodes of atrial tachycardia, alternating with periods of atrial arrest and a junctional escape rhythm. Therefore, a permanent ventricular pacemaker was implanted. The diagnosis of EDMD was made in 1984 and has since been confirmed by genetic studies, which have identified a unique mutation in the amino acid coding sequence of the disease gene.²

The patient's mobility gradually but progressively deteriorated; he now needs a wheelchair to travel distances greater than 200 yards, but is able to walk short distances. Pacemaker generator change has been complicated by infection, which required replacement of the pacing system, but there have been no other cardiac complications and he is still free from cardiac symptoms. However, recent echocardiography showed massive dilatation of the right atrium and, to a lesser extent, the right ventricle and left atrium (fig 2). He has been anticoagulated with warfarin, because of the risk of thromboembolism.

Case 2

The 27 year old nephew of case 1 was first seen when he was 3 years old, when he was observed to have generalised hypotonia and a marked lordosis. Over the next seven years he developed flexion contractures of both elbows and the achilles tendons. His achilles tendons were lengthened when he was 10 years old, and his right biceps tendon was lengthened when he was 17. Serial ECGs and echocardiography performed at clinic visits were normal.

Aged 17, he presented to his general practitioner complaining of palpitations and dyspnoea on exertion. An ECG showed a nodal

bradycardia of 50 beats/min. Ambulatory ECG monitoring showed sinus rhythm, alternating with long periods of nodal bradycardia; no tachyarrhythmia was observed. A ventricular demand pacemaker was implanted and he stayed well during the next five years. At routine follow up when he was 22 years old he was found to have atrial fibrillation. On questioning, the patient volunteered a history of transient episodes of visual disturbance which, possibly, could be of an embolic origin. He was anticoagulated, and successful cardioversion to sinus rhythm was performed. Shortly afterwards, his pacemaker was upgraded to a dual chamber system. Ten months later, he reverted to atrial fibrillation and has remained in this rhythm. To date, echocardiography has shown no evidence of chamber dilatation, and ventricular contraction remains normal.

Case 3

This 24 year old patient is the brother of case 2 and, because of family history, has been followed from an early age. Contractures of both elbows and achilles tendons, associated with a lumbar lordosis, were first observed when he was 6 years old. During the next two years, the contractures of his achilles tendons worsened, needing surgery to lengthen them. Routine screening ECGs were normal until he was 15 years old, when a junctional bradycardia was identified and a ventricular pacemaker was implanted. Clinically, he remains well, and is able to continue to work as a manual labourer. Serial echocardiography has shown no abnormality of chamber dimensions or contractility.

Discussion

EDMD is an X linked muscular dystrophy, characterised by muscle weakness and atrophy. It begins in childhood, often with the peroneal muscles, and progresses to the shoulder and pelvic girdles in the teenage years. It is associated with flexion contractures of the elbows, and cardiac conduction defects.³⁻⁶ Early cases were described in 1902, but the disease itself was first recognised in 1966.³ Progression of muscle weakness is much slower than in Duchenne muscular dystrophy, making mobility and employment into middle and late adult life possible for those affected. It can be distinguished from Becker muscular dystrophy by the distribution and natural history of the muscle weakness, the presence of contractures, cardiac conduction abnormalities, and the absence of pseudohypertrophy and intellectual impairment.⁴

The gene maps to Xq28,⁷ and was identified by Bione *et al* in 1994.⁸ It encodes a serine rich protein, emerlin, whose precise function is unknown. Emerlin is localised to the inner nuclear membrane in many cell types, and may be involved in anchoring the cytoskeleton to the membrane. In the heart, it is also localised to desmosomes and fasciae adherentes, which may account for the link between EDMD and cardiac conduction defects, as these structures are closely involved with cell to cell signalling.⁹ Most families analysed (including this family)

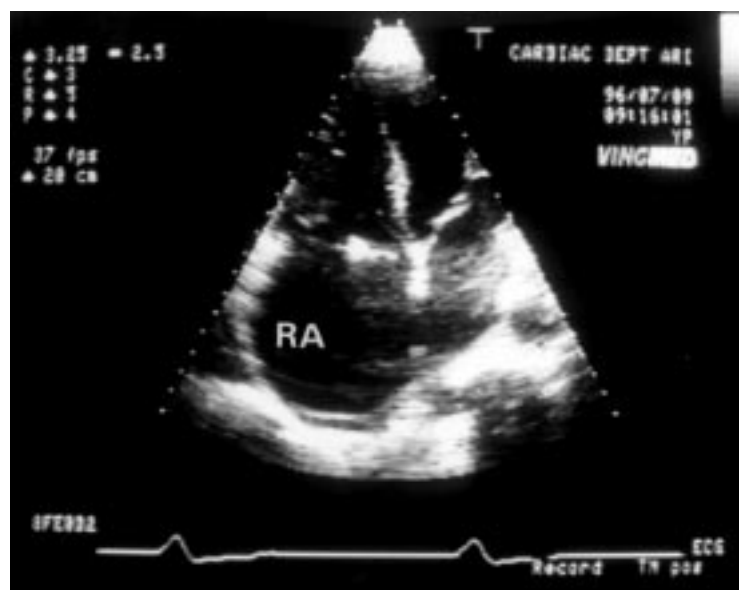


Figure 2 Transthoracic echocardiogram of case 1 (apical four chamber view) showing marked right atrial dilatation. The echodense area in the region of the tricuspid valve is due to reflected echoes from a ventricular pacing lead. RA, right atrium.

have had unique mutations,¹⁰ associated with reduced or absent emerin expression in the skeletal and cardiac muscle of affected patients, and reduced expression in female carriers.¹¹ Immunocytochemical analysis of emerin expression in skin or muscle may be helpful in confirming the diagnosis.¹¹

Classically, the mode of inheritance is X linked, but several families have been reported in which the EMD phenotype shows autosomal dominant inheritance, with male to male transmission.⁴

Serum creatine kinase activity is slightly raised in EDMD; the level usually peaks in childhood, and declines progressively from the second decade. Levels are not as high as those seen in Duchenne or Becker type muscular dystrophies. Creatine kinase levels are not useful in identifying carriers; in a study of 33 carriers, there was no significant increase in muscle enzymes or isoenzymes.¹²

Cardiac involvement in EDMD is common, and, when present, has been linked to a high risk of sudden death.¹³ The severity of the cardiomyopathy has no correlation with the degree of skeletal muscle involvement. Indeed, female carriers of EDMD (who have no skeletal muscle involvement) are at risk of developing cardiac involvement, and sudden (presumed cardiac) death has been reported in a female carrier.¹⁴

The risk of arrhythmia rises with age.¹⁵ In asymptomatic patients with early cardiac involvement, ECG may show low amplitude P waves with a prolonged PR interval. Subsequently, this may progress to atrial fibrillation or flutter. However, the most characteristic ECG is of junctional escape rhythm (40–50 beats/min) without obvious P waves, because of atrial standstill. The diagnosis is further strengthened by a failure to record an intra-atrial ECG, and failure to pace the right atrium or coronary sinus.¹⁶ This form of atrial paralysis is almost pathognomonic of the cardiomyopathy of EDMD. In an analysis of accumulated case reports of atrial paralysis, 33% of cases were attributable to EDMD.¹⁷ Therefore, a finding of isolated atrial paralysis should prompt careful clinical examination for the skeletal muscle anomalies present in EDMD; genetic and immunocytochemical analysis may also be appropriate.

Usually, the cardiomyopathy of EDMD affects the atria, and right heart involvement predominates. The reason for this is unknown, but may be because of the smaller muscle mass of the right heart. The normal myocardium is progressively replaced by fibrous and adipose tissue,^{14, 18} which results in the loss of atrial contractility (atrial paralysis) and atrial dilatation (which can be huge). In the later stages of EDMD, the ventricles may become involved in the disease process, leading to progressive ventricular dilatation and, ultimately, ventricular failure. For patients with atrial paralysis, treatment is ventricular pacing. These patients should also be anticoagulated as there is a high risk of intra-atrial thrombus formation and embolisation. Additionally, patients with clinically significant ventricular involvement may

benefit from diuretic therapy and ACE inhibition as appropriate. Heart transplantation has been used successfully in EDMD.^{19, 20}

EDMD is often referred to as a benign form of muscular dystrophy, because of the slow progression of skeletal muscle involvement. Corrective surgery can assist in preserving mobility and functional independence well into adulthood. However, as shown in this case series, cardiac problems may not be apparent until the teenage years or later; clearly these are not benign. When first reported,¹ the nephews of the index case did not have any evidence of cardiac involvement, but in both the disease has progressed to the extent that they need a pacemaker to control the bradyarrhythmia. Case 2 has also developed chronic atrial fibrillation, which may be associated with embolic events. In retrospect, the decision to upgrade his pacemaker to a dual chamber system was wrong; the natural history of the disease is for the atria to become unresponsive to electrical stimuli. The massive right atrial dilatation which developed in the index case has not, to our knowledge, been previously reported.

The cardiac risk associated with carriage of the genetic abnormality, and the variable expression of this abnormality, supports the need for screening of family members of index cases. Carriers of the genetic abnormality should have a resting ECG, 24 hour ambulatory Holter monitoring, and echocardiography. If cardiac involvement is confirmed, prophylactic pacing should be offered to obviate the risk of sudden death due to bradyarrhythmia. In the absence of any identifiable abnormality, the optimal frequency of repeat screening remains unclear.

We thank Dr Kevin Jennings for permission to report this series of patients.

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IMAGES IN CARDIOLOGY

Cutting balloon for treatment of severe peripheral pulmonary stenoses in a child

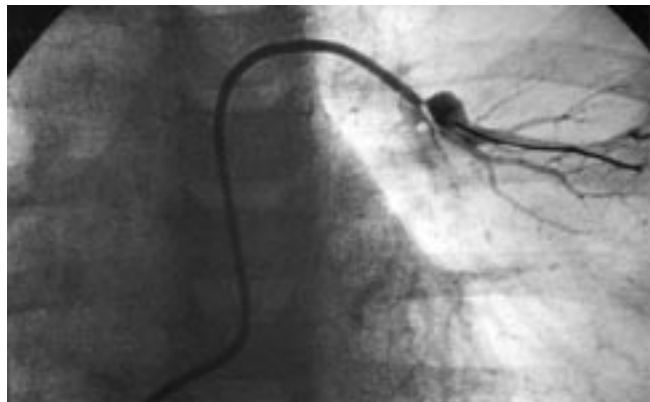
A male infant underwent successful dilatation of supra-valvar pulmonary stenosis at which time additional multiple peripheral pulmonary artery stenoses were identified. Three separate attempts were made to dilate these using balloon inflation pressures up to 20 atmospheres. Many lesions resisted inflation and right ventricular pressure remained suprasystemic. At 2.5 years old these stenoses were dilated using a 3.75 mm cutting balloon system followed by a 4 mm coronary high pressure balloon. The left figure is a selective angiogram within the left pulmonary artery showing a tight stenosis. The right figure is the final angiogram. After dilatation of several resistant stenoses the right ventricular pressure fell from 115 to 60 mm Hg.

The cutting balloon system consists of an angioplasty balloon with four longitudinally mounted microsurgical

blades at 90° angles, which deploy when the balloon is inflated. The inflated diameters of the balloons range from 2 to 4 mm (0.25 mm increments) and the balloon lengths range from 10 to 15 mm. The working height of the atherotomes is from 0.127 to 0.152 mm. This system has been described in the management of resistant coronary lesions¹ and demonstrated in an animal model of peripheral pulmonary stenoses.² To our knowledge this is the first description of the use of a cutting balloon for this application in a child.

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