

X linked muscular dystrophy with contractures

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SUMMARY Another family with X linked muscular dystrophy affecting particularly the humeral and tibial muscles is described. Cardiomyopathy in the eldest male necessitated the insertion of a pacemaker.

The Becker form of X linked muscular dystrophy is now well recognised, but other benign forms have occasionally been described. Dreifuss and Hogan in 1961¹ and then Emery and Dreifuss² studied a kindred from Virginia, concluding that this family represented a new type of X linked muscular dystrophy with limb girdle involvement and flexion contractures, but without pseudohypertrophy. A few other similar families have been reported, often with sufficient differences in the distribution of muscle weakness for some authors to conclude that their family represents a distinct syndrome.³ Rowland *et al.*,⁴ on the other hand, considered that there was simply one variety. We report another such family with X linked muscular dystrophy and cardiomyopathy.

Case reports

CASE 1 (II.3 FIG 1)

Case 1 was born on 9.5.54. He did not walk until about 15 months of age when he tended to walk on tip-toes. At the age of 9 he was unable to dorsiflex his feet beyond a right angle and contractures at the elbows were noted three years later. By 19 he had marked wasting and weakness of his biceps and triceps. Although there was some wasting of both thigh and calf muscles, power was normal, but no tendon reflexes were obtained. He had ichthyosis, a

depressed sternum, and thoracic kyphosis with absence of lumbar lordosis. Examination at the age of 24 showed a myopathic facies with bilateral ptosis and wasting and weakness of the sternomastoids. Limited flexion of the neck was also noted. The shoulder girdle muscles and triceps were wasted and weak and the biceps markedly wasted and weak (fig 2). There was normal power of the forearm and

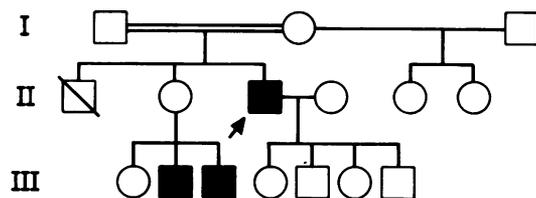


FIG 1 Pedigree.

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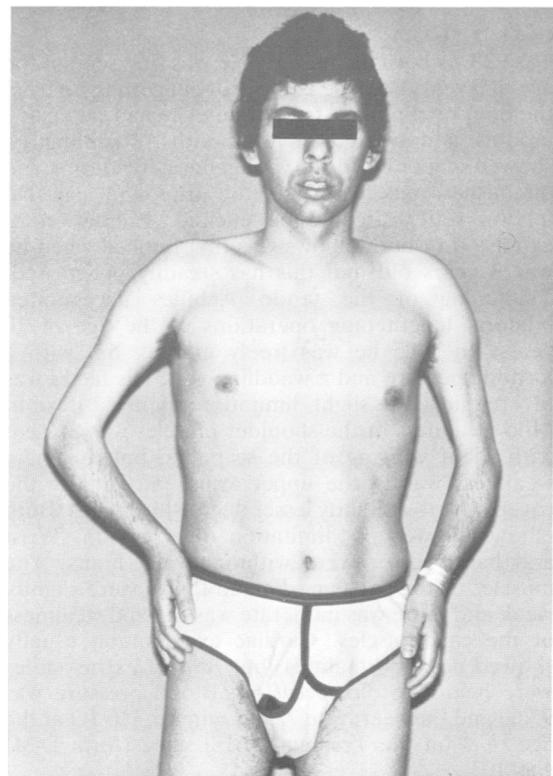


FIG 2 Proband showing myopathic facies, wasting of humeral muscles, and flexion contractures of elbows.

small muscles of the hands. The thigh muscles were moderately weak and wasted. There was marked wasting and weakness of the calf muscles with contraction and pes cavus such that he had to stand on tip-toes. He had been working at a Remploy factory and in 1984 underwent bilateral Achilles tenotomy. Examination later that year showed further progression, including slight winging of the scapulae. Extension of the elbow was limited to 100° on the right and 120° on the left. The forearm muscles were of good bulk and power, but abduction of the fingers was slightly weak. He had difficulty in sitting and rising from a chair. There was marked wasting of the calf, peroneal, and anterior tibial muscles with moderate reduction in power. Extensor digitorum brevis was preserved on both sides. The muscle consistency was normal, as was sensation. No pseudohypertrophy had been noted at any stage. Colour vision was normal. His blood pressure was 110/70. The heart sounds were normal, but his pulse was slow and irregular before the implantation of a pacemaker in September 1984 (Dr K Jennings). The steroid sulphatase level in a skin biopsy was normal (Dr D Broadhead).

CASE 2 (III.2)

Case 2 was born on 26.3.71. He was first seen at the age of 3 years because of difficulty in getting up from the floor or climbing stairs, though he had sat up at 6 months and walked at 14 months. Examination showed marked lordosis with general hypotonia and diminished muscle bulk in the arms and legs. No tendon reflexes could be elicited. Limitation of extension of both elbows was first noticed when he was 8 years old and this has steadily progressed. Tightening of the tendo Achilles necessitated bilateral lengthening operations at the age of 10 years. In 1985 he was freely mobile, but with a lordotic posture and a waddling gait. His facies was myopathic with slight limitation of neck flexion. Mild weakness of the shoulder muscles was present with slight winging of the scapulae, but the main weakness was in the upper arms, particularly the triceps and to a slightly lesser degree the biceps. Both elbows showed 60° limitation of extension. Wrist and hand power were within normal limits. The muscles of the pelvic girdle and thighs were slightly weak and there was moderate wasting and weakness of the calf muscles. Cardiac examination usually showed no abnormalities, but runs of extrasystoles were heard on one occasion. Blood pressure was 95/60 and the heart rate 72 per minute. His IQ at the age of 4 on the Terman-Merrill scale (form L-M) was 103.

CASE 3 (III.3)

Case 3 was born on 4.10.73 and was followed as an

outpatient because of the family history. Clinical examination and CK estimation (42 IU/l) were normal at the age of 14 months, but five months later the CK was 84 IU/l, rising steadily thereafter. Clinical examination remained normal until some winging of the scapulae and lumbar lordosis were noted at the age of 5. Limitation of elbow extension was found some six months later and at the age of 8 years lengthening of both tendo Achilles was required. Examination in 1985 showed marked lumbar lordosis and a slightly waddling gait. Neck movements were full. The shoulder muscles showed slightly reduced power, the triceps and biceps were clearly weak and wasted, the wrist flexors and extensors were of marginally reduced power, and the hand grip was good. In his pelvic girdle and legs there was slight weakness of the hip and thigh muscles and moderate weakness of the calf muscles. Like his brother, he has difficulty in getting up from the floor and climbing stairs. Tendon reflexes could not be elicited in the arms and the knee jerks could only just be elicited in the legs. Elbow extension was deficient by 30° on both sides. Cardiac examination showed no abnormality. Blood pressure was 95/55 and heart rate 68 per minute.

Carrier females

None of the obligatory or possible carrier females (I.2, II.2, II.6, III.1) showed any evidence of muscle weakness or alteration in the tendon reflexes. In only I.2 was there cardiac disease, atrial fibrillation being discovered at the age of 56. Rheumatic heart disease had been questioned during pregnancy at the age of 40, but a cardiologist concluded that her heart was probably normal. An ECG then was said to be normal, but review has shown varying A-V dissociation. There is no history of unexplained deaths or early cardiac deaths in obligatory or possible carriers.

Family history

Although the proband's parents are first cousins, the development of the disease in his sister's sons strongly suggests X linkage. She is not related to her husband.

Investigations

CK LEVELS

CK investigations are given in the table. The relatively low levels in the affected males should be noted, while those in the obligatory carriers average just below the upper limit of normal, though in II.2 the earlier levels were normal.

TABLE CK levels in affected males and presumed and possible female carriers.

Pedigree No	Case	Date of birth	1974-1976	1978-1980	1981	1984-1985
II.3	1	9.5.54	426	686		775,486
III.2	2	26.3.71	139 (av)			486 (av)
III.3	3	4.10.73	42.84	172 (av)		312
I.2		1.5.24		47 (av)		45 (av)
II.2		10.6.48	17	23 (av)		64 (av)
II.5		3.9.61		41 (av)		
II.6		10.7.64		20 (av)		77
III.1		31.3.69	25	25	46 (av)	

The normal range is less than 50 μ l.

MUSCLE BIOPSIES

The biopsy from the right pectoralis major muscle taken from case 1 at the age of 30 showed slight proliferation of sarcolemmal nuclei with the internalisation of nuclei and variation in fibre size. Type 1 fibres were predominantly affected without significant grouping (fig 3). The biopsy taken in case 2 when aged 3 from the right gastrocnemius also showed random variation of muscle fibre size with many necrotic, basophilic fibres and numerous central nuclei. No hypertrophied fibres were present.

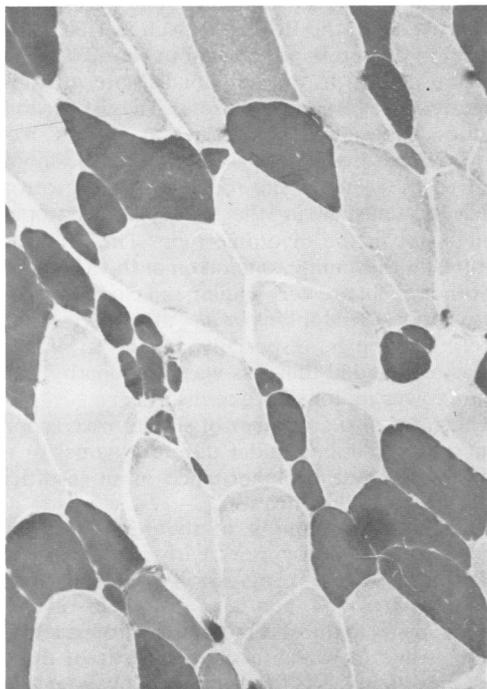


FIG 3 Muscle biopsy from case 1 showing variation in fibre size and atrophy of type 1 fibres. (ATP-ase at pH 4.3.)

ELECTROPHYSIOLOGICAL STUDIES

Nerve conduction studies have been carried out in case 1 in 1973, 1978, and again in 1984 using the right peroneal nerve on each occasion and also the ulnar or median nerve. The results are consistently within normal limits. Left biceps, right triceps, rectus femoris, vastus medialis, and tibialis anterior were used for EMG studies either in 1978 or 1984. All were silent at rest and on effort showed a normal interference pattern.

ELECTROCARDIOGRAPHY

In case 1, an earlier ECG at the age of 19 had shown atrial tachycardia with variable block. Before insertion of the pacemaker, a high degree of AV block had developed with pauses of up to 2.8 seconds. The ECG in case 2 showed sinus rhythm with a short PR interval and non-specific T wave changes in the septal leads, while in that of case 3 marked sinus arrhythmia with a variable PR interval was present. ECGs performed on the carrier females were normal with the exception of I.2, already mentioned, and possibly of II.6 who had non-specific inverted T waves in V1-4 and of III.1 with short PR interval.

ECHOCARDIOGRAPHY

Echocardiography was normal in all those examined (I.2, II.2, II.3, II.5, III.1, III.2, III.3), except for the index case and his mother. The first echocardiogram in case 1 at the age of 28 was normal with normal cardiac size. A year later there was a suggestion of dilatation of the right side of the heart with an altered contraction pattern of both ventricles, compatible with an early dilated cardiomyopathy. A third echocardiogram six months later showed global reduction in contraction of the left ventricle which was of normal size, while the right ventricle was hyperkinetic. His chest x-ray showed cardiomegaly (CTR 54%). In I.2, echocardiography revealed global reduction in contraction of the normal sized left ventricle and a hyperkinetic right ventricle, again compatible with cardiomyopathy.

CYTOGENETIC STUDIES

The karyotype of the proband was 46,XY in peripheral blood and skin cultures.

Discussion

The syndrome described in 1966 by Emery and Dreifuss² involved the proximal muscles, initially of the pelvic girdle. Flexion contractures at the elbows and shortening of the tendo Achilles, mild pectus excavatum, and absence of calf pseudohypertrophy were other characteristic features. In some there was facial weakness, while cardiac involvement was noted in the oldest four of the seven patients. Sparing of the distal muscles was emphasised, though in the original report of Dreifuss and Hogan¹ moderate weakness and wasting distally in the legs was noted in one patient.

Thomas *et al.*³ whose family showed predominant involvement of the scapular and distal leg muscles, had concluded that this was a quite different disease, although there were certain similarities. However, one of their patients also showed weakness of quadriceps and hamstring muscles.

Other authors have included under the term of Emery-Dreifuss syndrome patients with distal weakness. Rowland *et al.*⁴ reported a sporadic case with scapular winging and wasting and weakness of the deltoid, biceps, and triceps with the legs being normal, except for slight weakness of anterior tibial and peroneal muscles. Nevertheless, they considered that there was only one syndrome. Hopkins *et al.*⁵ referred to the Emery-Dreifuss 'humeroperoneal' muscular dystrophy with marked wasting and weakness of the peroneal muscles in the legs of their index patient. Dickey *et al.*⁶ described two patients as having weakness that was more pronounced proximally in the arms and distally in the legs, while a third had proximal weakness as well. They emphasise the diagnostic pattern of early contractures in the absence of major weakness, a point noted in this family also. Facial involvement was present in all affected males. The distinction, then, between the Emery-Dreifuss, scapulohumeral, and other similar forms of muscular dystrophy is not entirely satisfactory, since it appears to be based mainly on the extent of involvement of the distal, as opposed to the proximal, muscles of the lower limbs and to a lesser extent also on the biceps and triceps being more affected than the scapular muscles. Yet shortening of the tendo Achilles, often requiring surgery, is characteristic. Part of the apparent variation may be purely descriptive, in that the musculature generally is poor, so that detailed comparisons of the weakness and wasting become difficult. It appears that in most families there is one

person with both proximal and distal wasting and weakness in the legs. Facial weakness may be more definite in the Emery-Dreifuss syndrome.

Evidence of abnormality appears in childhood, although relatively minor and only slowly progressive, so that, in the absence of a family history, diagnosis may be difficult. The contractures, particularly at the elbows, are an early and potentially valuable clue to the diagnosis. Absence of pseudohypertrophy is another characteristic feature.

The later development of cardiomyopathy may not be recognised, unless specifically sought. Conduction defects in our index case eventually led to the insertion of a pacemaker. The changes in the ECGs of his nephews may prove to be relevant, although their echocardiograms are still normal. In retrospect, the atrial tachycardia in our index case at the age of 19 was probably significant. Waters *et al.*⁷ noted the association of dystrophic and cardiac features. Dickey *et al.*⁶ emphasised not only the atrial conduction defects, often leading to death by mid-adulthood, but also stated that there was a substantial risk to female carriers. That is not evident in this family.

Various authors^{3,5} have discussed the difficulty of distinguishing between a myopathic and neurogenic disorder. Hopkins *et al.*⁵ commented that the EMG did not show the classic myopathic features in every muscle. Indeed, the EMGs (as well as ENG) were normal in our proband, though in case 2 at the age of 3 the pattern in the left tibialis anterior muscle suggested a myopathic process. The ECG abnormalities, especially the conduction defects, would also favour a myopathy. Both the muscle biopsies from cases 1 and 2 showed type 1 fibre atrophy which is unusual in the muscular dystrophies, though not in the myotonic type. The histological features in this family, one taken at the age of 3 and the other at 30, are very similar and closely resemble those reported. Hopkins *et al.*⁵ after reviewing the differing findings, especially in the EMGs and ENGs, concluded that this was a myopathy, rather than a lower motor neurone disorder.

There are also a number of similar case reports,⁸ sometimes described under different names or with a different mode of inheritance or in insufficient detail to allow classification.

The features common to the reports reviewed here are childhood onset, early development of contractures, slow progression with absence of pseudohypertrophy, and later cardiac involvement. What appears to differ is the muscle groups affected. The distribution which is characteristic of this and most other families is the striking involvement of the muscles attached to the humerus and tibia, so that the humerotibial form would perhaps be the most

appropriate as well as a more descriptive name. Whether there are indeed two or more distinct forms, or whether the full range of the one syndrome has not yet been delineated, is uncertain at present. Analogy with other disorders would suggest heterogeneity as the more likely explanation. Proof that they are identical, allelic, or different should come from recombinant DNA studies.

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