An unusual family of benign 'X' linked muscular dystrophy with cardiac involvement

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Summary. A family of benign X-linked muscular dystrophy is described. Two of the 3 affected members appear quite representative of Becker's dystrophy. A third shows no pseudohypertrophy, only gross atrophy, affecting proximal and distal muscles and also shows early onset contractures and electrocardiographic abnormalities and is in these ways much more representative of the variety described by Emery and Dreifuss (1966). Two of the cases have distinctly abnormal electrocardiograms with extensive and deep Q waves and abnormal R/S ratios in VI. Both these have shown progression of electrocardiographic abnormalities during a 2-year follow-up. The family is reported to document this very unusual occurrence.

In 1955 Becker and Keiner first described a benign form of X-linked dystrophy. Since then several other apparently different X-linked benign dystrophies have been described. The benign nature of these is only relative to Duchenne, for in several cases disability becomes quite severe by the fourth and fifth decade, and deaths may occur earlier from cardiac involvement (Thomas, Calne, and Elliot, 1972; Rothhauve, Mortier, and Bayer, 1972).

This paper records a family of benign X-linked dystrophy which cannot be fitted among the forms so far described. Additionally, we have been able to record evolution of electrocardiographic abnormalities not generally available before.

The family tree is outlined in Fig. 1. Thirteen family members have been examined personally. Electrocardiographic, electromyographic, and CK values are recorded. Muscle biopsies are available from 3 affected cases.

Case reports

Case 1 (III.12). A man aged 25 years was well till the age of 12 when he experienced difficulty in climbing up the stairs. He noticed hypertrophy of the buttocks and calves by the age of 15 to 16 years. He was unable to stand by 17 to 18 and was chair-bound by 20. When examined at the age of 27 the patient could sit up from lying down position only with help. He could maintain the sitting posture, with support only.

On examination the power in his hip and shoulder girdle muscles was grade III. The power in the distal muscles of both the extremities was good (grade IV to V). There was hypotonia of the limbs, wasting of arms and shoulder girdle, and pseudohypertrophy of the hip and calf muscles. All the reflexes were sluggish. The electrocardiogram showed a small Q wave in lead I, II, III, aVF, and V4 to V6. The algebraic sum of R + S in V1 was -3 and the axis was +60°.

The CK was 175 sigma units. The electromyogram showed small thin potentials with a full interference pattern diagnostic of myopathy. Muscle biopsy confirmed the diagnosis showing rounding of fibres, variations in fibre size, and increase in interstitial tissue. Central nuclei were prominent.

Case 2 (III.3). A man aged 36 years was well till the age of 15 years when he started falling down while walking. The weakness was progressive so that by the age of 17 to 18 he had to have support while standing up from the sitting posture, but till the age of 20 he was able to cycle. Up to the age of 32 he was still able to stand; at that age he fell down and sustained a fracture of the left tibia and fibula and now he cannot stand. At present he can sit up from the lying down position with some support.

On examination the power in his shoulder and pelvic girdle muscles was grade II and that of the distal muscles grade IV. All reflexes were absent. There was hypertrophy of the calves (Fig. 2). He had minimal shortening of the achilles tendon on the left side.

His CK was 205 sigma units in June 1973; in May 1975 it was 46 sigma units (upper limits of normal for our laboratory is 24 sigma units). Clinically, the

FIG. 1

FIG. 2. Case 2 (a) Appearance of shoulder girdle musculature and (b) pseudohypertrophy of calves.

cardiovascular system was normal but the electrocardiogram in June 1973 showed distinct Q waves in II, III, aVF, and V4, V5, and V6. There was an R_sR^1 pattern in V1 and the algebraic sum of R + S in V1 was +5 mV.

The electrocardiogram was repeated in May 1975. It again showed Q waves in II, III, aVF, V4, V5, and V6, R_sR^1 in V1, with R + S sum +6 mV. A new development was definite ST elevation in V1 and V2 not seen before. The axis was +190°.

Case 3 (III.9). The man aged 23 years first noticed trouble after being bed-ridden after a fall at age 15 years. Between the ages of 16 and 17 the calf muscles remained normal ? pseudohypertrophic, but from the age of 18 he began having distinct atrophy of all the muscles and developed contractures of both elbows, both knees, and both hips from the age of 18 to 19 years of life.

On examination the pelvic and shoulder girdles had power grade III only. There was pronounced wasting of all the muscles including the forearm and leg, with serious degree of contractures of the elbow, knee, and

hip joints, with shortening of the achilles tendon. All the reflexes were absent. Fig. 3 shows the gross wasting which affected proximal and distal musculature and the contracture. His CK was 159 sigma units. Muscle biopsy confirmed the diagnoses of myopathy with all the classical features (rounding of fibres, variation in fibre size, and central nuclei). The interstitial tissue was much increased.

Electrocardiogram in June 1973 showed Q waves in II, III, aVF, V4, V5, V6, and R + S sum in V1 was -1. When repeated in May 1975, R + S sum was +6 with an R wave of 15 mm. The Q waves remained the same.

Case 4 (III.27). The patient, 10 years old, has just begun complaining of having frequent falls during walking. We have not seen this patient.

Case 5 (I.2). The grandfather started having trouble from age of 32. The daughter is sure that the disease was similar to that of the above-mentioned patients. He was chairbound by the age of 52 to 53 and died at the age of 55 after fever. He also had pseudohypertrophy.

FIG. 3. Case 3 (a) Gross atrophy involving arm and forearm, and (b) absence of pseudohypertrophy: this was the maximal extension of knee joint possible on either side.

Seven additional male and 3 female members were examined. The mother II.2 an obligate carrier aged 55 had a CK of 20 units. III.11 appears to be a carrier as her resting CK was 95 units.

Discussion

This is apparently a family of X-linked muscular dystrophy of late onset and relatively slow progression. In Table I are listed the features of the different muscular dystrophies so far described as X-linked.

In addition Rotthauwe *et al* (1972) recently described another family of X-linked dystrophy as a separate entity. The presence of early onset, early

contractures, slow progress, and absence of any pseudohypertrophy suggest to us that it is similar to the entity described by Thomas *et al* (1972).

In Table II, we have listed the findings in our cases for comparison with Table I.

Our Cases 1 and 2 appear to resemble Becker's variety, while our Case 3 with his gross generalized atrophy, both proximal and distal, and early contractures, seems to resemble the variant described by Emery and Dreifuss (1966) more than Becker's though the onset is in the second decade. According to Mabry *et al* (1965) the variety described by them has distinctive muscle biopsy findings not seen in any of our cases.

TABLE I
X-LINKED MUSCULAR DYSTROPHIES

	Age at Onset (y)	Distribution	Pseudohypertrophy	Cardiac Muscle Involvement	Contracture	Course
Duchenne	5	Girdle	++++	+++ 80%	Late	Death around 20
Becker and Keiner (1955)	5-25	Pelvifemoral	++	?	None	Benign
Emery and Dreifuss (1966)	3-5	Pelvifemoral	None; atrophy marked	+	Early	Benign
Mabry <i>et al</i> (1965)	11-13	Pelvifemoral	++	+	Absent	Benign slow disability
Thomas <i>et al</i> (1972)	Early	Scapulo-peroneal	None	Late	Elbow; pes cavus	Slow; cardiac death common
Van Vijnngaarden, Bethlem, and Barth (1974)	Congenital	Girdle	None	None	None	Early death before 5 y

TABLE II
FEATURES OF PRESENT CASES

Case No.	Present Age (y)	Age of Onset	Age became Non-ambulant	Pseudohypertrophy	Heart Involvement	Contractures	CK (Sigma units)
1	27	12	20	++	?	None	175
2	36	15	33	++	++	None	205 (age 34) 46 (age 36) 150
3	25	15	19	nil	++	+++	—
4	10	10		--	--	--	--

TABLE III
CARDIAC FEATURES IN BENIGN X-LINKED DYSTROPHY

	Age at Onset of Electrocardiographic Abnormality	R/S in V1	Blocks	Arrhythmia	Tall R in LV Leads	Ischaemic Heart Disease Type	Clinical Heart Disease
Emery and Dreifuss (1966)	after 20	NR	? yes	++	0	?	Yes
Mabry <i>et al</i> (1965)	—	1/4	+	0	0	+ ST only	No
Thomas <i>et al</i> (1972)	after 15	NR	mild	++	Not recorded	Present	Yes

LV—Left ventricular. NR, not recorded.

Cardiac involvement in benign X-linked dystrophies. In three of the benign forms of X-linked dystrophy cardiac involvement is well recognized (Table III).

Systematic studies on the electrocardiogram in Becker's dystrophy are sparse (Emery, 1972). Becker's initial cases had no cardiac involvement. Emery (1972) has studied 14 cases and studied the R-S in V1 and found it abnormal only in one case. 'No more than expected by chance.' He did not report on any other changes. Other electrocardiographic abnormalities have been reported occasionally. Zellweger and Hanson (1967) described one case with right ventricular hypertrophy and one with biventricular hypertrophy. Nisipeanu and Dimitriu (1974) described abnormal Q waves in V6 and one of the 3 sibs had an R/S ratio of 1.2 in V1. Ueda *et al* (1970) described left ventricular hypertrophy in 2 cases with abnormal Q waves in I, aVL, V4 to V6 in one. The RS sum in V1 was -11 in one, and -1 in the other. Becker himself now believes that in the cases included under his eponym about 25 per cent show electrocardiographic abnormalities (1973, personal communication).

Against this, 2 of our 3 patients showed large Q waves in leads II, III, aVF, and V4 to V6. One of the patients also had an interventricular conduction defect. The algebraic sums of R + S in V1 in our patients were 6 and 5, respectively. Another feature of the present report is the development of

the electrocardiographic abnormalities. Though these abnormalities are an early feature of Duchenne's dystrophy they are apparently static and do not progress (Slucka, 1968). Most reports we have seen of the changes in the benign forms record only a single electrocardiogram in each case. In contrast in Case 3 (III.9) the R + S sum in V1 changed from near normal (-1) to grossly abnormal (+6) in 2 years (R/S ratio changed from 0.9 to 1.66), the other cases showing the appearance of an elevated ST-T segment of at least 2 mm in the right chest leads not present before. This has occurred without any evidence of clinical myocardial infarction.

Significance of cardiac involvement in X-linked dystrophy. It is surprising that five X-linked dystrophies have frequent cardiac involvement while the several autosomal dystrophies very uncommonly affect the heart. (The exception is myotonic dystrophy which has several non-muscular features.) The matter would be more easily explained if all the X-linked dystrophies were allelic and Mabry *et al* (1965) have suggested this. It has been shown, however, on the basis of linkage with colour blindness, that at least the genes for Becker and Duchenne's dystrophy are not allelic (Skinner, Smith, and Emery, 1974) and to our knowledge no evidence of allelism among the others exists.

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