Short report

An unusual familial muscle disorder

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SUMMARY Autosomal dominant inheritance of an unusual muscle disease is reported in a family. The pathological appearance, of regularly arranged markedly atrophic muscle fibres without other evidence of disturbed innervation, are similar in each case. However, the onset of the disease, its distribution and its progression has varied within the family.

Inherited muscle diseases commonly present with a pattern of weakness either in the limb-girdle (LG), facioscapulohumeral (FSH), or scapuloperoneal (SP) distribution, each of which may be due to a variety of underlying pathologies.^{1,2}

A family is reported in which the distribution of weakness did not readily conform to any of these clinical patterns, where the age of onset and rate of progression of the disease was variable within the family, and where the biopsy appearance, although consistent within the family, did not conform to any established nosological entity.

Case histories and results

Case reports

The autosomal dominant nature of the inheritance is shown in fig 1.

Case 1 (III, 3: born 2 July 1942) This patient suffered from a slowly progressive proximal limb-girdle weakness which had been present from about age 25 years. This had always been painless and there was no increase in symptoms with exercise. There was no history of cramps, fasciculations or myoglobinuria. Examination in 1981 showed a moderate symmetrical proximal upper and lower limb-girdle myopathy. There was no rash or history of dysphagia.

Case 2 (II, 3: born 11 September 1913) This patient had a 10 year history of proximal upper and lower limb-girdle weakness. Her early life had been normal and relatively

athletic. She had first become aware of difficulty rising from a low chair in her late 50s and had attributed this to "the family problem". She did not spontaneously seek medical advice but agreed to further investigation.

Case 3 (II, 5: born 19 July 1912) This patient had a five year history of slowly progressive lower limb-girdle weakness to the stage of difficulty with stairs and low chairs. There was no history of upper limb weakness, pain, cramps, fasciculations or myoglobinuria.

Case 4 (III, 1: born 28 January 1938) This patient complained of proximal weakness in the lower limbs only, of 6 years duration. The weakness was mild and did not interfere with his occupation.

Case 5 (I, 3: Died aged 70 yr) This patient had developed proximal weakness of both upper and lower limb-girdles in her 50s. This was slowly progressive to the point of requiring a wheel chair by the age of 66. She died at age 70 from myocardial disease. No further details of this patient could be obtained.

Fig 1 Family tree, affected individuals in filled circles or squares

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Case 6 (II, 1; Died aged 47 yr) This patient developed proximal weakness of the lower limb-girdle only, at the age of 44. There was little progression over the ensuing 3 years and he was able to continue with his employment. He was killed in an unrelated road traffic accident. No further details of his muscle disease have been obtained.

Case 7 (I, 7; Died aged 69 yr) This patient developed late onset upper and lower limb-girdle weakness at about the age of 65 years. She died four years later from myocardial disease. The weakness impaired her ability to climb stairs but was never severe. No further details of her muscle disease have been obtained.

Case 8 (IV, 1; aged 16 yr) This patient, is thought by the family to exhibit proximal lower limb-girdle weakness. However she also has brain damage from birth. Permission to carry out an examination was denied.

In the four members of the family who have been studied investigations have shown normal FBC, ESR, biochemical

profile, ECG, echocardiogram and pulmonary function tests. The CK has been elevated in each between 197 and 445 IU/l (normal < 120 IU/l). Nerve conduction studies showed no evidence of a neuropathy. EMG studies have shown similar findings in each case with marked insertional activity, fibrillation and positive sharp waves. The units were small in amplitude with only occasional units of greater than 1 mV and were polyphasic. Occasional pseudo-myotonic bursts were seen in each patient. In case 4, where the weakness was confined to the lower limb-girdle, the EMG showed similar appearances in the clinically uninvolved asymptomatic upper limb muscles.

Computed tomography

CT of the muscle was undertaken according to a standard protocol.³ The scans were abnormal in each case and showed similar appearances, however, the severity of the abnormality varied between patients. The abnormalities were those of multiple small low density areas with preservation of the fascial planes and muscle outlines. Case 1 showed the most

Fig 2 Cryostat sections of quadriceps from case 1 (d) and case 2 (a-c) stained with H&E showing scattered atrophic fibres with dense nuclear clumps (a-d), myofibres possessing internal nuclei (a, b, d) and a ragged-red fibre (b). Thin ribbon-like atrophic fibres are also visible in (b) and (d). Note the extensive fatty connective tissue in (d). Bar = 50 μ m.

Table Muscle biopsy data

Case	Age at biopsy y	Non-muscle component* %	Fat %	Type I %	Internal nuclei %	Small fibres %	Fibre diameter μm $\bar{x}$ CV%	Fibre CSA μm^2 $\bar{x}$ CV%	Fibre shape $\bar{x}$ CV%
1	39	17.3	15.7	75	28.0	24.3	45.3 86	4470 119	0.79 17
	40	8.0	28.0	—	14.8	17.4	55.7 59	5134 85	0.81 25
2	68	10.8	5.2	60	22.4	32.8	45.9 85	4910 114	0.74 18
	75	15.0	0	60	32.3	30.0	40.4 79	3808 106	0.72 20
3	70				poor specimen (no morphometric data)				
4	44	18.0	0	89	11.8	32.3	52.5 71	5694 90	0.75 20

*Excluding fat. Fibre size data from 100 contiguous fibres in each biopsy. CSA = cross-sectional area.
 $\bar{x}$ = arithmetic mean. CV% = coefficient of variation.

marked changes, the muscles of the leg, the quadriceps and the psoas muscles being uniformly involved. The other three cases only showed abnormalities in the leg muscles and the psoas. In Case 2 there was a suggestion of some involvement of the erector spinae muscles.

The CT appearances of the muscle were similar to those seen in the early stages of adult or adolescent spinal muscular atrophy.⁶

Muscle biopsies

Quadriceps muscle biopsy samples were obtained from cases 1–4 and processed for histochemistry.^{5–7} Material from case 4 was also processed for electron microscopy. The histological composition, muscle fibre size and shape, and fibre type distributions were estimated as described elsewhere.^{10–12}

Muscle biopsy appearances

In each specimen fascicular and muscle fibre architecture was normal except for the presence of internal nuclei and regularly scattered severely atrophic muscle fibres with rounded profiles (fig 2). In two cases there was fatty replacement of muscle fibres although other connective tissue components were not increased. In all cases many of the atrophic fibres contained clumps of pyknotic nuclei and derangement of fibrillar material which were confirmed on electron microscopy. Ultrastructural abnormalities of neuromuscular junctions suggestive of denervation were also observed. Many of the remaining fibres appeared mildly hypertrophic. 1–2% of fibres showed excessive basophilia.

Morphometric data are given in the table where the marked variation in fibre size (CV%), increased fat component, and the similarity in mean fibre size and shape between samples may be noted. There was a predominance of type I fibres in each sample though there was no tendency to type grouping. Analysis of 100–500 fibres from each specimen showed between one-third and two-thirds to have pathological features (internal nuclei or extreme atrophy, see table).

Discussion

This family is unusual with respect both to its clinical presentation and to its pathological features.

In most inherited neuromuscular diseases (apart from myotonic dystrophy) the age of onset of the disorder is relatively constant within the family¹¹ which is in marked contrast to this family where the

age of onset has varied from adolescence to middle age. Again the course of most neuromuscular disorders is usually constant within a family.¹¹ The pattern of the neuromuscular disease does not easily fit with any of the common clinical presentations of neuromuscular disorders.^{12–13}

An unusual form of focal distal spinal muscular atrophy has been described^{13–14} with evidence of focal weakness and wasting of muscle confined to the distal extremities predominantly of the lower limb. This has a relatively slowly progressive course but is commonly sporadic. The rate of progression and relatively benign nature of the myopathy in this family has similarities to focal distal spinal muscular atrophy except in its distribution.

Pathologically, despite the wide variation in age at the time of biopsy, the appearances were remarkably similar. This would not be an expected finding in, for example a family with spinal muscular atrophy or myotonic dystrophy where the pathological features are progressive with age.^{15–16} In the one family member studied where there was a 7 year gap between the biopsies there was very little change pathologically which again would not be expected in most neuromuscular diseases.

The characteristic pathological feature throughout was the occurrence of numerous markedly atrophic fibres, with pyknotic nuclei, widely dispersed throughout the biopsy. Occasional ribbon-like atrophic fibres were also seen. In spinal muscular atrophy the characteristic findings are those of denervation, usually the presence of scattered ribbon-like atrophic fibres in the early stages of the disease with progression to groups of ribbon-like atrophic fibres with time, and signs of reinnervation as manifested by groups of uniform fibre type.¹⁵ Thus the pathological findings in this family are markedly different from those seen in spinal muscular atrophy. However, in some patients with long-standing spinal muscular atrophy, occasional small fibres with clumps of densely staining pyknotic nuclei are seen in areas that otherwise show the pathological features typical of spinal muscular atrophy^{7 15 17 18} (and Cumming, *et al* unpublished observations). It is

suggested that such fibres in the present family had also undergone long-term denervation. This is supported by ultrastructural evidence of end-plate disruption. That this represents denervation alone rather than part of the denervation/reinnervation cycle of spinal muscular atrophy is corroborated by the absence of pathological signs of reinnervation and the EMG findings. It would also seem probable that the denervation was sporadic, occurring within single motor units, to account for the spatial distribution of the abnormal fibres.

It is suggested therefore that this family displays a myopathy, of autosomal dominant inheritance and varied clinical progression, characterised by limited denervation predominantly in the muscles of the lower limbs, with a relatively benign prognosis. Current evidence does not support the inclusion of this family's disorder in any previously established nosography.

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