

Atypical Histopathological Changes in Muscle Biopsies from Two Patients with facioscapulohumeral Muscular dystrophy

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Abstract

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disorder with an estimated prevalence of 1:20000, clinically defined by a characteristic regional distribution of progressive muscular weakness. It is associated with partial deletions of a 3.3 Kb tandem repeat on human chromosome 4q35. Histopathological changes in FSHD are not uniform. Myopathic, inflammatory and “neurogenic” alterations have been described, as well as the presence of lobulated and moth-eaten fibres. We describe the cases of two patients with FSHD who presented atypical histopathological findings in muscle biopsy. The first patient was a 52 years-old man with a facio-scapulo-peroneal distribution of muscular weakness and moderately increased serum CK whose quadriceps muscle biopsy revealed the presence of abundant nemaline (rod) bodies, cytoplasmic bodies and “ragged red” fibres. The second patient was a 58-year-old man with facial and asymmetrical scapular muscular weakness and slightly increased serum CK whose quadriceps muscle biopsy disclosed marked increase of lipids in most fibres, with normal carnitine levels. In both patients DNA analysis confirmed the diagnosis of FSHD demonstrating fragments of respectively 30 and 24 Kb originating from 4q35. Our observation confirms that the histopathological features of FSHD are not uniform and that atypical features can be found..

Keywords: FSHD, muscle biopsy, rods, lipid storage.

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Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common hereditary disease of muscle, with an estimated prevalence of 1:20000 [13]. It is inherited as an autosomal dominant disorder and it is clinically defined by a characteristic distribution of progressive muscular weakness. Typical is the early involvement of facial and scapular muscles, followed by eventual spreading to pelvic and lower limb muscles, with the foot extensors often affected earlier and more severely than pelvic muscles. Clinical severity is highly variable, even within the same family, with some patients showing only minimal signs of the disease and others (approximately 15-20%) [10,21] becoming wheelchair-bound.

Genetic linkage of FSHD has been established to human chromosome 4q35 [24]. Most cases of FSHD are associated with partial deletions of a 3.3 Kb tandem repeat (D4Z4) that can be detected by EcoRI restriction fragments shorter than 35 Kb [23,25]. However, no transcribed sequences have been identified within the tandem repeat array, and the pathophysiology of FSHD remains obscure.

Relatively little has been written about histopathological changes in FSHD. Most biopsies from patients with FSHD show myopathic changes, namely variation in fibre diameter, centrally placed nuclei, occasional necrosis of muscle fibres and increase in endomysial and perimysial connective tissue [17]. The presence of large and small fibres associated with an increase in the mean fibre diameter of all types has been described [5]. Because of the regional distribution of muscle involvement, the changes in muscle biopsy may vary considerably depending on the site of sampling. Most clinically involved muscles may show advanced histologic changes, with replacement by adipose or collagenous connective tissue [17]. Fibres may have a lobulated appearance, due to reorganization of the intermyofibrillar network [1,17]. Moth-eaten fibres, showing focal decrease of oxidative enzyme activity, have been described [7,17]. Angular atrophic fibres are commonly found, randomly scattered or showing some grouping [2,5,17]. In some cases, infiltrates of mononuclear cells may be detected in perivascular distribution or in perimysial and endomysial connective tissue [9,16]. In

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some instances, these inflammatory changes may be striking.

We describe the cases of two patients with genetically confirmed FSHD and “atypical” histopathological findings on quadriceps muscle biopsy.

Case reports

Case 1

The patient was referred to us at the age of 52. Since 50 he had been complaining of difficulty walking, due to foot drop. Clinical examination revealed stepping gait, mild weakness of facial muscles with difficulty whistling, wasting and weakness of upper girdle muscles with scapular winging and weakness of the dorsiflexors of the ankle. Serum creatine kinase was moderately increased (400 U/l, with normal values within 190 U/l).

The patient underwent open-muscle biopsy of the right quadriceps muscle. Hematoxylin and eosin staining showed moderate variation of fibre diameter, with small and normal-sized fibres, and mild increase in connective tissue (Fig. 1). Gomori's trichrome revealed the presence of nemaline (rod) bodies in several fibres (Fig. 2). Most of these fibres were atrophic. Also cytoplasmic bodies in scattered degenerating fibres and some “ragged red” fibres were observed. With oxidative enzyme reactions some fibres showed disorganization of the cytochemical architecture and increase in enzyme activity. Cytochrome c oxidase was normally distributed. Electron microscopic examination confirmed the presence of rods. Mitochondria appeared normal.

DNA analysis was performed on blood leucocytes. Double digestion with EcoRI/BlnI and Southern blot analysis with the p13E-11 probe (D4F104S1 locus) demonstrated a fragment of 30 Kb, confirming the clinical diagnosis of FSHD.

Case 2

The patient was observed for the first time at the age of 58. He complained of weakness in his right arm. Clinical examination showed wasting and weakness of the upper girdle muscles with limitation of abduction and anteflexion of the right arm, asymmetric scapular winging and

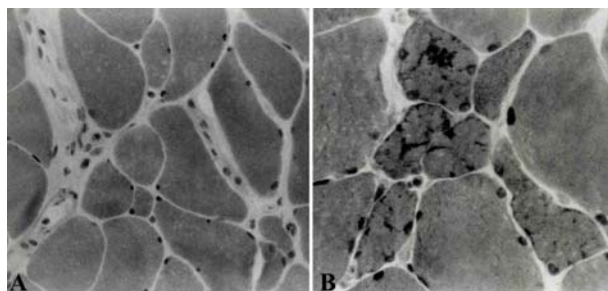


Figure 1. Case 1. Muscle biopsy demonstrates: a), fibre size variability and mild increase in connective tissue. H&E, 265X; b), nemaline (rods) and cytoplasmic bodies. Gomori's trichrome, 420X.

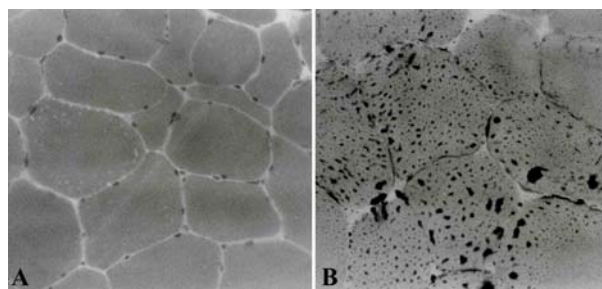


Figure 2. – Case 2. Muscle biopsy demonstrates: a), fibre size variability and small angular fibres. H&E, 265X; b), increase of lipid contents in most fibres. Sudan Black B, 420X.

mild facial weakness. Serum CK was slightly increased (200 U/l, with normal values within 190 U/l).

The patient underwent open-muscle biopsy of the right quadriceps muscle. Hematoxylin and eosin and Gomori's trichrome showed moderate fibre size variability, some atrophic angular fibres and one necrotic fibre invaded by macrophages. With oxidative enzyme reactions no alteration was observed. Sudan Black B revealed marked increase of lipids in most fibres. Muscle carnitine was within the normal range.

DNA analysis was performed on blood leucocytes. Double digestion with EcoRI/BlnI and Southern blot analysis with the p13E-11 probe (D4F104S1 locus) demonstrated a fragment of 24 Kb, thus confirming the clinical diagnosis of FSHD. The same alteration was found in one of the patient's daughters, a 30-year-old woman who presented a mild phenotype with moderate weakness of facial muscles and dorsiflexors of the ankle.

Discussion

Although FSHD is one of the most common muscular dystrophies, relatively little has been written about its histopathological features. Apart from myopathic changes [17], neurogenic features (mainly small angular fibres, often with some grouping) [2,5,17] and inflammatory changes [9,16] have been described. Moreover, alterations of the inner structure of muscle fibres, such as lobulated [1,17] or moth-eaten [7,17] fibres, may be observed.

The most impressive change observed in case 1 was the presence of rods (nemaline bodies) in a relatively large number of fibres. Rods originate from Z-disks and contain Z-line proteins like α -actinin. They tend to cluster under the sarcolemma and around nuclei and predominate in type I fibres. They are the main distinctive feature of the so-called nemaline myopathy, a term that encompasses a heterogeneous hereditary group of disorders with different clinical and genetic characteristics [8]. Different mutations have been described in patients with nemaline myopathy, indicating a disease of muscle sarcomeres and, in particular, of thin filaments. Among the involved proteins are α -tropomyosin [12], α -actinin [18], nebulin [19], troponin T1 [11] and β -tropomyosin [4]. Apart from the classic nemaline myopathy, rods have been described also in other genetic and acquired myopathies, such as

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central core disease [22,20], multiple acyl CoA deficiency [15], alcoholic myopathy [14], HIV-infection [3,6] and polymyositis (personal observation). In these cases rods can be considered a non specific degenerative change. Up to date rods have never been described in FSHD. Thus, the abundance of nemaline bodies observed in case 1 represents an atypical finding. As all the possible causes of acquired myopathy with nemaline bodies, including HIV-infection, were excluded in our patients, rods can be interpreted as a degenerative alteration.

Also an increase in lipid content like that observed in case 2 has never been reported in FSHD. In the literature there are no data suggesting an alteration of lipid metabolism in FSHD. Carnitine levels in muscle were normal, thus excluding the most common causes of lipid storage myopathy. Like rods, also lipid increase can represent a peculiar aspect of degeneration.

Our observation confirms that histopathological changes in FSHD are not uniform and that atypical features can occur.

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