Autosomal dominant congenital fibre type disproportion: a clinicopathological and imaging study of a large family


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Congenital fibre type disproportion (CFTD) is considered a non-progressive or slowly progressive muscle disease with relative smallness of type 1 fibres on pathological examination. Although generally benign, CFTD has a variable natural course and severe progression has been observed in some patients. The pathogenesis of the disorder is unknown and many authors consider CFTD a syndrome with multiple aetiologies rather than a separate clinical entity. A positive family history has been reported in about 40% of cases, but the inheritance pattern is not clear. Both autosomal recessive and dominant modes of inheritance have been suggested. The present paper describes a large, multigenerational kindred that has an inherited myopathy fulfilling the histological criteria of CFTD, with autosomal dominant transmission and high penetrance. The clinical picture, remarkably similar in all affected family members, started in early infancy with mild limb muscle weakness. There was slow progression of symptoms into adulthood, with moderate to severe, mainly proximal, muscle weakness without loss of ambulation. Muscle biopsy from two affected individuals demonstrated predominance of small type 1 muscle fibres without other significant findings. Nerve conduction studies were normal and needle electromyography showed a myopathic pattern. MRI examination performed on three patients from successive generations showed involvement of proximal limb and paraspinal muscles. The clinical and pathological homogeneity in the present family, together with the lack of additional histological abnormalities after decades of disease progression in two affected individuals, supports this being a distinct myopathy with fibre type disproportion. Whether the disease in this family can be regarded as a form of the congenital myopathy known as CFTD or rather a unique condition sharing histological features with CFTD needs further investigation. This is, to our knowledge, the largest kindred with muscle fibre type disproportion reported to date. Our data confirm autosomal dominant inheritance, and this is the first MRI document of this disorder.

Keywords: congenital fibre type disproportion; congenital myopathy; muscle MRI; autosomal dominant

Abbreviations: CFTD = congenital fibre type disproportion; DTR = deep tendon reflex


Introduction

In 1973 Brooke coined the term ‘congenital fibre type disproportion’ (CFTD) to describe a disorder of skeletal muscle with weakness and hypotonia present at birth or shortly thereafter, generally slow or absent progression of motor symptoms and frequent skeletal abnormalities, including congenital hip dislocation, joint contractures, foot deformities and kyphoscoliosis (Brooke, 1973). The characteristic histochemical pattern on muscle biopsy consists of a predominance of type 1 fibres, which are at least 12% smaller than type 2 fibres, the latter being normal or hypertrophic.
Congenital fibre type disproportion (Brooke, 1973; Fardeau et al., 1975; Cavanagh et al., 1979). Sporadic and familial cases—consistent with both autosomal dominant and recessive inheritance—have been reported (Brooke, 1973; Kinoshita et al., 1975; Curless and Nelson, 1977; Eisler and Wilson, 1978; Jaffe et al., 1988). However, the diagnostic criteria, histopathological features and clinical course of the disease are still insufficiently defined. Furthermore, the existence of CFTD as a separate disorder has remained controversial, since type 1 fibre hypotrophy can also be encountered in other neuromuscular conditions. In a recent review, Clarke and North (2003) identified 67 cases in the literature, supporting the retention of CFTD as a distinct nosological entity. Mutations in the α-skeletal actin (ACTA1) gene have been identified recently in severe cases of CFTD, but the molecular mechanisms leading to disproportion in fibre size are unknown (Laing et al., 2004). Whether ACTA1 mutations can also lead to milder cases of CFTD needs to be investigated.

In the present paper we describe a multigenerational non-consanguineous family with a dominantly transmitted neuromuscular disease in which 25 members were available to us for clinical evaluation. Pathological examination of muscle performed in two affected individuals showed predominance of small type 1 fibres and an increase in diameter of type 2 fibres without any other remarkable changes. In addition, detailed electrophysiological and muscle MRI studies were undertaken in several individuals. To our knowledge, this is the largest CFTD kindred reported to date.

**Methods**

**Patients**

The kindred reported here (Fig. 1) was first identified when the index case was referred to the neurology outpatient clinic for evaluation of muscle weakness. A thorough description of the pedigree and personal and clinical data on deceased or absent individuals were obtained by a series of clinical interviews. Twenty-five family members were personally interviewed and examined by one of us. Laboratory workup, chest X-ray, electrocardiogram and echocardiogram were performed in the propositus and two additional patients. Semithin sections were stained with toluidine blue and ultrathin electron microscopy were fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide and embedded in Epon after routine dehydration. Tiny rectangular pieces for histochemistry and another for electron microscopy. The first piece was snap-frozen in liquid nitrogen-cooled isopentane and transverse 7 μm cryosections were performed with or without atrophy.

**Electrophysiological studies**

Detailed electrophysiological investigations were performed in five patients. Motor and sensory nerve conduction and late responses were evaluated using standard procedures (Kimura, 1989). Concentric needle electromyography, including turns/amplitude (T/A) and multi-motor unit potential analyses were performed in proximal and distal limb muscles (Stalberg et al., 1983; Bischoff et al., 1994). In addition, single-fibre EMG was performed in at least one muscle from each patient (Stalberg and Trontelj, 1994).

**MRI studies**

Three patients underwent MRI evaluation of muscle. These studies were performed with a 1.5 T field strength magnet (GE Signa Horizon LX 9.2) using T1-weighted and Short tau inversion recovery (STIR) sequences in the axial plane. Scans of the scapular girdles and arms, pelvic girdle and thighs were obtained for each individual. Scan parameters for T1-weighted images were: repetition time 400 ms; echo time 18 ms; matrix 512 × 224; one acquisition; section thickness 10 mm; intersection gap 1 mm; field of view 400–480 mm. STIR sequences were performed as follows: repetition time 11250 ms for shoulder and pelvic girdle studies and 3500–6500 ms for thigh studies; echo time 37.7 ms, inversion time 150 ms; matrix 256 × 256; one acquisition; section thickness 10-mm; intersection gap 1 mm; field of view 400–420 mm.

**Muscle biopsies**

Open deltoid muscle biopsies were performed on patients V-14 and VI-1 at the ages of 43 and 25 years, respectively. Specimens were oriented and each was divided into two pieces, one for histochemistry and another for electron microscopy. The first piece was snap-frozen in liquid nitrogen-cooled isopentane and transverse 7 μm cryosections were performed in 2.5% glutaraldehyde, postfixed in osmium tetroxide and embedded in Epon after routine dehydration. Semithin sections were stained with toluidine blue and ultrathin

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**Fig. 1** Genealogy of the family. Generations are labelled with Roman numerals and the individual members with Arabic numbers. Each member examined is indicated with an asterisk. Black = affected; white = unaffected; dark grey = probably affected by history; light grey = probably unaffected; question mark = affection status unknown.
sections were contrasted with uranyl acetate and lead citrate and mounted in copper grids. Ultrathin sections were examined with a Philips CM100 electron microscope. Random fields of muscle sections stained with ATPase at pH 9.4 were examined for fibre type identification and histometric analysis. The same procedure was followed at pH 4.63 and 4.35 for type 2 fibre subgroup characterization. The computer program Leica IM 1000 Image Manager V1.2, Leica Microsystems AG, Switzerland was used to record the measures, and a histogram of both muscle biopsies was constructed measuring the lesser fibre diameter (maximum diameter across the lesser aspect of the muscle fibre) of 300 fibres in each case. The mean fibre diameter, standard deviation and percentage of each fibre type were also calculated.

Molecular genetic analysis

DNA from two affected members and one unaffected family member was purified from peripheral blood leukocytes using standard procedures. We performed PCR amplification followed by bidirectional sequencing of all ACTA1 coding exons. Previously published primers and conditions were used for exons 2 and 4–7 (Nowak et al., 1999; Ilkovski et al., 2001). exon 3 was amplified with the primer pair E3F, 5'-AGACAAGAAGCGGAGAAG-3'; E3R, 5'-GCAGGAGATGTGGTGG-3'. Fifty nanograms of genomic DNA was mixed with 0.4 μM of each primer, 200 μM of each deoxynucleotide, 1.5 mM Cl2Mg, 4% DMSO and 0.15 U of Taq polymerase at 72°C for 3 min, followed by five cycles of 30 s at 94°C, 30 s at 66°C and 45 s at 72°C, after which 34 additional cycles were performed, of 30 s at 94°C, 30 s at 64°C and 45 s at 72°C, followed by a final 4 min extension at 72°C.

Results

Pedigree analysis

The family pedigree is shown in Fig. 1. The first ancestor known to be affected by this condition was II-1, who had been born in Galicia (northwestern Spain). Interviewed family members believed the disease had been transmitted by individual I-2, who was also of Galician origin. There was no knowledge of consanguinity in the family. Analysis of the inheritance pattern throughout the pedigree suggested an autosomal dominant gene with high penetrance. There was no excess of affected individuals of either sex (13 affected women and 11 affected men). Male-to-male, female-to-female, male-to-female and female-to-male disease transmission were all present. There was no instance of disease transmission from unaffected parents.

Case reports

Out of 25 individuals available to us for examination (indicated with an asterisk in Fig. 1), seven showed signs of myopathy. The clinical findings of affected subjects are summarized in Table 1.

Case V-14 (index case)

The propositus, a 54-year-old woman, was the only child of non-consanguineous parents. Her mother, who had a previous miscarriage, had muscle weakness from infancy (case IV-10 described below). Her father died at age 54 without having shown neuromuscular symptoms. The patient was born after a full-term pregnancy and normal delivery. Intrauterine movements were recalled by her mother as normal. She was a somewhat floppy infant but had otherwise no respiratory or feeding difficulties and no significant motor milestone delay. She could stand at about 8 months and walk at around 12 months. However, from her early childhood she had a clumsy gait and difficulty getting up from the floor. During her school years she was a slow runner and jumped clumsily. She had no language or learning disability. Muscle strength decayed slowly in the subsequent decades, with stepwise progression during her three pregnancies. By her fifties she was able to walk with difficulty, especially when carrying weights. She occasionally used a cane and had frequent falls on uneven floor. She could not stand up from a sitting position or climb stairs without support. She also noticed moderate weakness in the upper limbs. She had no respiratory difficulties, dysphagia or visual complaints. She reported no muscle pain, cramps, paraesthesiae or other sensory symptoms. She had three full-term, uneventful pregnancies and one miscarriage. On clinical examination she had normal stature and mild hyperlordosis, but no scoliosis. Muscle wasting mainly

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Finger ext</th>
<th>Wrist flex/extension</th>
<th>Forearm flex/extension</th>
<th>Arm extension/abduction</th>
<th>DTR = deep tendon reflexes</th>
<th>Proximal wasting</th>
<th>Gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-10</td>
<td>F/80</td>
<td>4+</td>
<td>4+</td>
<td>5/4</td>
<td>3</td>
<td>4</td>
<td>4+4</td>
<td>4–/4+</td>
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<td>IV-26</td>
<td>F/80</td>
<td>4–</td>
<td>4+/-4</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4/3</td>
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<td>5</td>
<td>5/5</td>
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<td>4</td>
<td>4</td>
<td>5/4+</td>
<td>4+4+</td>
</tr>
<tr>
<td>V-14</td>
<td>F/54</td>
<td>5</td>
<td>4+</td>
<td>5/4</td>
<td>4</td>
<td>4</td>
<td>4–/4+</td>
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<td>M/27</td>
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<td>4</td>
<td>5/4+</td>
<td>4+4+</td>
</tr>
<tr>
<td>VI-15</td>
<td>F/29</td>
<td>5</td>
<td>4+/-4</td>
<td>4–</td>
<td>5</td>
<td>4</td>
<td>5/4+</td>
<td>4+4+</td>
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<td>M/28</td>
<td>5</td>
<td>4+/-4</td>
<td>4–</td>
<td>5</td>
<td>4</td>
<td>5/4+</td>
<td>4+4+</td>
</tr>
</tbody>
</table>

M = male; F = female; abd = abduction; add = adduction; flex = flexion; ext = extension; dorsif = dorsiflexion; DTR = deep tendon reflexes. Muscle strength was graded using the Medical Research Council scale. Muscle groups not included in the table were normal in all individuals. Deep tendon reflexes are classified as absent (0), hypoactive (1–2) or normal (3). Muscle wasting was graded from absent (–) to severe (+++).
affected the deltoid and triceps muscles in the upper limbs, as well as the quadriceps muscles in the lower limbs (Fig. 2A, upper panel). She had moderate weakness of hip flexor and extensor muscles, quadriceps, foot and toe dorsiflexors, deltoid, triceps and extensor carpi muscles. Her gait was waddling and steppage. Extraocular, facial and neck muscles showed normal strength. Her speech was normal. There was no joint hyperlaxity, myotonia, fasciculations or pyramidal signs. She had no high-arched palate, pes cavus or other dysmorphic features. Deep tendon reflexes (DTRs) were hypoactive in the upper limbs, absent at the knee and preserved at the ankle. Fundoscopic examination, cerebellar and sensory systems as well as language and other cognitive functions were normal. Laboratory results were within normal limits, including thyroid function, pyruvate, lactate, liver enzymes, serum aldolase, lactate dehydrogenase and creatine kinase. Chest X-ray, echocardiogram and ECG were unremarkable. Nerve conduction studies were normal, thus ruling out a peripheral neuropathy. Concentric needle EMG showed myopathic changes. Results are summarized in Table 2. A muscle biopsy taken from her right deltoid and MRI studies are described below in detail.

Case IV-26 (Fig. 3)
No prenatal data were available on this currently 80-year-old patient. As far as she knew, her mother’s pregnancy and delivery had been unremarkable. Muscle weakness was first noted in early childhood, with clumsiness on getting up, running and climbing stairs. Weakness had been slowly progressive and affected lower and upper limbs, without ocular, face or bulbar muscle involvement. At the time of examination she was severely disabled. She needed a walker to get around her house and could not climb stairs. Although with great difficulty, she was still able to get up from a chair by herself, alternately using nearby furniture and her own thighs as support. On examination she had severe weakness and atrophy affecting the proximal lower limbs (mainly gluteus, psoas, hamstring, quadriceps and tibialis muscles) and upper limbs (most severely the arm elevator and rotators, deltoid, biceps and triceps muscles), with mild involvement of more distal muscles, such as the extensor carpi and lumbricals. Her speech was normal, as were the cranial nerves, sensory and cerebellar functions. DTRs were all absent except for the ankle jerk. She had hyperlordosis and mild dorsal kyphosis, but otherwise no dysmorphic features and no joint hyperlaxity could be disclosed.

Case VI-1
This 27-year-old male was born at term following an uncomplicated gestation. No problems were detected in the newborn period, he was not noticed to be hypotonic, and his crying and sucking were good. His motor milestones were slightly delayed, he frequently slipped when sitting, he had difficulty crawling and he was able to cruise at 18 months. He had frequent falls in early childhood and at school he was a poor runner and clumsy at sports. He had difficulty getting up from the floor, which he achieved with a brisk impulse. Speech development and intelligence were normal. Progression of muscle weakness in recent years had been unremarkable. On clinical evaluation he had an independent walk, with mild waddling and bilateral foot drop. He could stand up from a sitting position with his arms crossed, although with some instability. He was able to climb up and down
the stairs without support but he could not run down the stairs. There was mild proximal upper limb weakness, mainly affecting arm elevator and triceps muscles. Bicipital, tricipital and knee DTRs were absent. The styloradialis reflex was hypoactive but present bilaterally and ankle jerks were normal. He had numerous scars from a juvenile acne conglobata but otherwise no skin or joint abnormalities were detected. He had normal height, a poor general muscle development, mild hyperlordosis, and his face was somewhat long and thin. However, the face and neck muscles had normal strength. The extraocular muscles and cranial nerves were normal, as were the sensory and cerebellar systems. Laboratory tests, including glucose, urea, creatinine, uric acid, liver enzymes, total serum protein, albumin, cholesterol, triglycerides, Na, K, Ca, P, alkaline phosphatase, lactate dehydrogenase, creatine kinase, aldolase, thyroid function, lactate and pyruvate, were all normal. Electrocardiogram results were also normal. Nerve conduction studies were

<table>
<thead>
<tr>
<th>Case</th>
<th>Muscle examined</th>
<th>Fibrillation/PSWs</th>
<th>Multi-MUP analysis</th>
<th>Polyphasia</th>
<th>Turns/amplitude</th>
<th>Fibre density</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Amplitude µV (REL SD)</td>
<td>Duration ms (REL SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-2</td>
<td>Biceps</td>
<td>++</td>
<td>441 (0.5)</td>
<td>9.5 (-0.3)</td>
<td>++</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior</td>
<td>++</td>
<td>1019 (2.2)</td>
<td>8.2 (-2.6)</td>
<td>N</td>
<td>1.8</td>
</tr>
<tr>
<td>V-14</td>
<td>Biceps</td>
<td>++</td>
<td>505 (1.1)</td>
<td>6.9 (-2.1)</td>
<td>Myopathic</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior</td>
<td>++</td>
<td>508 (-0.4)</td>
<td>7.4 (-3.2)</td>
<td>Myopathic</td>
<td>1.7</td>
</tr>
<tr>
<td>VI-15</td>
<td>Biceps</td>
<td>++</td>
<td>302 (-1.9)</td>
<td>8.3 (-1.6)</td>
<td>Myopathic</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior</td>
<td>+</td>
<td>398 (-1.3)</td>
<td>9.3 (-1.7)</td>
<td>Myopathic</td>
<td>1.7</td>
</tr>
<tr>
<td>VI-16</td>
<td>Biceps</td>
<td>++</td>
<td>359 (-0.3)</td>
<td>6.8 (-2.1)</td>
<td>Myopathic</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior</td>
<td>++</td>
<td>694 (0.8)</td>
<td>7.4 (-3.2)</td>
<td>Myopathic</td>
<td>1.7</td>
</tr>
</tbody>
</table>

PSW = positive sharp wave; MUP = motor unit potential; REL SD = relative standard deviation; + = discrete; ++ = moderate; +++ = abundant.

Fig. 3 Photographs of individuals IV-26 and IV-24. The 80-year-old patient (IV-26, arrow) has pronounced proximal muscle atrophy compared with her 82-year-old unaffected sister.
normal and needle EMG (tibialis anterior muscle bilaterally, right biceps, deltoid, right vastus medialis) disclosed a myopathic pattern without spontaneous activity. A muscle biopsy was obtained from his left deltoid.

Additional family members
Significant findings on clinical examination of other affected family members are summarized in Table 1. Case IV-10, the 80-year-old mother of the propositus, showed no problems in the newborn period and could stand and walk at the appropriate age. However, she had difficulty running and going up and down stairs since early childhood. Her gait had always been ‘peculiar’. She subsequently developed a slowly progressive muscle weakness, including moderate upper limb weakness and difficulty carrying weights. At the time of examination she was unable to stand up from a chair without help. Her gait was waddling. She could take a few independent steps but generally used a cane and had frequent falls. She had no dysphagia or problems with language or respiration. Moderate weakness and wasting of the proximal limb muscles was evident. Facial and extraocular muscles, sensory and cerebellar function were normal.

Individual V-2, the 57-year-old father of VI-1, was born after an uncomplicated pregnancy with normal intrauterine movements. He was not regarded as a floppy child, could breathe and suck normally, and early developmental milestones were unremarkable. In his early school years, however, he was slower and clumsier than other children. He had no progression of weakness until his fifties, when he started to notice some worsening of muscle strength. With time his walking and running had become clumsier and his ability to lift weights was somewhat poorer than expected for his age. Upon clinical examination he showed mild proximal limb weakness and difficulty with foot and toe dorsiflexion (Fig. 2B). However, he could get up from a low seat and could climb up and down stairs without support. He was tall, had mild hyperlordosis and a long, thin face with no dysmorphic features. Facial and neck muscle strength was normal, as were his intelligence, speech, cranial nerves, sensory and cerebellar tests. Routine laboratory workup, including creatine kinase, was normal.

Patient VI-15 is the oldest daughter of the index case. She did not show any complications during early infancy and could cruise at 9 months. Motor difficulties were first noticed by age 2 years. By that time she had difficulty getting up from the floor or from a kneeling position and was a clumsy runner. Although reading was delayed, speech and mental development were otherwise normal. On examination at age 28 he showed proximal limb wasting (Fig. 2A, lower panel) and had difficulty climbing up stairs while holding moderate weights. He had no muscle pain or limb numbness. Cranial nerves and facial and neck muscle strength were normal. He had mild hyperlordosis, waddling gait and difficulty with heel walking. Neurophysiological examination was performed in patients V-2, VI-15 and VI-16; results are shown in Table 2.

All other evaluated family members showed no abnormality upon neurological examination. Individual VI-19 had a somewhat clumsy gait, but no weakness or muscle atrophy was noticed. She could jump, squawk and run up and down the stairs without difficulty. Non-examined, probably affected individuals were identified by report of other family members as having an abnormal walk and poor muscle performance from infancy. The disease could be traced back two generations before the oldest living individuals. The first family member known to be affected (II-1) had shown progressive gait problems and clumsiness most of her life. Her father was thought to suffer from similar symptoms, but this could not be confirmed by currently living relatives.

Electrophysiological studies
Nerve conduction and electromyographic studies were performed in patients V-2, V-14, VI-1, VI-15 and VI-16. Nerve conduction studies, including F waves and distal latencies, were normal. Concentric needle EMG showed scattered fibrillations and positive wave potentials at rest. Mild voluntary effort easily recruited short-duration, low-amplitude motor unit potentials, pointing to a primary muscle disorder. This was further documented by multi-motor unit potential analysis. Single fibre density was normal in all cases. Table 2 summarizes the electromyographic findings of cases V-2, V-14, VI-15 and VI-16.

MRI studies
Affected individuals from three generations were available for MRI of muscle. MRI study of patients IV-10, V-14 and VI-16 at 80, 54 and 28 years of age, respectively, demonstrated bilateral and symmetrical muscular involvement. At the shoulder girdles and upper thorax, VI-16 showed moderate loss of volume and fatty infiltration of paraspinal muscles, and discrete loss of volume without fatty infiltration of rotator cuff muscles in both shoulders. A more advanced disease stage could be seen in V-14 as an increase of intramuscular fat and atrophy, especially in the paraspinal muscles, and a decrease of muscle volume in the shoulder girdles and chest wall. In late stages, as seen in IV-10, there was generalized atrophy affecting all muscles.

Early paraspinal lumbar muscle involvement was seen in VI-16. An oedema-like pattern was present on STIR sequences as diffuse hyperintensity of muscle bellies with normal
appearance on T1-weighted images. This oedema-like pattern was also noticed in case V-14, together with moderate fatty infiltration and decrease in muscular bulk. Symmetrical glutei involvement was seen in case VI-16 as patchy areas of increased signal intensity on STIR images, and discrete fatty infiltration as linear deposits of intramuscular fat on T1-weighted images. Progressive and generalized involvement of the pelvic girdle was seen in V-14 and IV-10 with marked muscular atrophy. Thigh involvement was also bilateral and symmetrical, with slow progression of the disease throughout the generations. In VI-16, patchy areas of hyperintensity were present on STIR images and there was also a linear pattern of fat deposition in adductor and hamstring muscles. Subtle changes in muscle signal intensity could be seen in both quadriceps, especially in the vastus lateralis. Interestingly, the gracilis muscles were spared and the semitendinosus muscles were less affected than the rest of the hamstring muscle group (Fig. 4A and B). These changes were more prominent in V-14 (Fig. 4C and D), with marked atrophy and fatty infiltration of the quadriceps (especially the vastus intermedius and lateralis) and adductor magnus. The posterior compartment of the thigh was less severely affected than the anterior muscle group. Gracilis muscles were still spared, and there was also relative sparing of the rectus femoris, sartorius, adductor longus and semitendinosus. Diffuse and marked atrophy could be seen in IV-10 (Fig. 4E), also affecting the gracilis and hamstring muscles, but to a lesser degree than in the vasti and adductor magnus.

**Muscle pathology**

Light microscopy examination revealed similar findings in both biopsies (Fig. 5). General tissue architecture was preserved. Although muscle fibres were generally polygonal in shape, some of the smaller fibres had rounded contours. Subsarcolemmal nuclei were unremarkable with no internal nucleation. Connective tissue was not increased and there was no fatty infiltration. Figures of degeneration, necrosis,
myophagia or inflammation were not observed. Oxidative enzymes demonstrated a regular myofibrillar network on both type 1 and type 2 fibres. Two distinct fibre populations were identified, randomly distributed among the fascicles. Histochemical staining revealed that all small fibres were of type 1 and the largest fibres invariably corresponded to type 2, most of these being 2A fibres. These findings were consistent with the diagnosis of congenital fibre type disproportion. Both histograms (Fig. 6) showed a predominance of type 1 fibres, the smallest belonging to type 1 and the largest to type 2. In the propositus, type 1 fibres accounted for 78.5% of fibres and had a mean diameter of 24.21 ± 5.46 (SD) µm, whereas type 2 fibres had a mean diameter of 55.23 ± 8.18 µm. In patient VI-1, type 1 fibres constituted 84.1% of fibres, with a mean diameter of 33.30 ± 8.21 µm and the mean diameter of type 2 fibres was 72.32 ± 16.04 µm. The diameter of type 1 fibres was thus 56.17 and 53.96% smaller than the mean diameter of type 2 fibres in cases V-14 and VI-1, respectively. Electron microscopic examination was unremarkable except for fibre size discordance. Myofibrillar structure and organization were normal in both fibre types, as were nuclei and mitochondria. The plasma membrane was not abnormally folded in small fibres, and the basal membrane was of normal appearance.

**Molecular genetic analysis**

No mutations were identified in the coding sequence of the *ACTA1* gene in affected subjects from the present kindred.

**Discussion**

The clinical features of the family reported here suggest progressive myopathy of a relatively benign nature. The only finding on muscle examination of two affected individuals was a disparity in size between type 1 and 2 muscle fibres, the characteristic pathological feature of CFTD. The diagnosis of CFTD requires selective smallness of type 1 muscle fibres, with a difference greater than 12% between the mean diameters of type 1 and type 2 fibres (Brooke and Engel, 1969; Brooke, 2005).
1973). Type 2 fibre hypertrophy has been described in some cases (Brooke, 1973; Cavanagh et al., 1979; Ter Laak et al., 1981). Because fibre size disproportion can sometimes be observed in muscle biopsy in addition to other distinctive abnormalities, the existence of CFTD as a separate diagnostic category remains controversial (Martin et al., 1976; Brooke et al., 1979; Cavanagh et al., 1979). Type 1 fibre predominance can often be observed in nemaline and centronuclear myopathies (Karpati et al., 1970; Radu and Jonescu, 1972). Other congenital myopathies, as well as other neuromuscular and central nervous system disorders, can also show relative type 1 fibre hypotrophy and must be ruled out in order to establish a diagnosis of CFTD (Clarke and North, 2003). A number of patients initially diagnosed with CFTD were later shown to have other, distinct neuromuscular disorders (Cavanagh et al., 1979; Martin et al., 1976; Dehkargarhani et al., 1981; Glick et al., 1984). It has been proposed that, in order to avoid confusion, a diagnosis of CFTD should be reserved for those cases with no other histological changes but a disproportion in size of type 1 and type 2 muscle fibres (Jaffe et al., 1988). Additional muscle abnormalities are generally not found in CFTD except for an excess of central nuclei and occasional rod-like formations (Caille et al., 1971; Brooke, 1973; Cavanagh et al., 1979; North, 2003). Intersample differences have been emphasized in previous reports (Cavanagh et al., 1979). In addition, a disproportion in fibre size up to 25% can be normal at certain ages (Polgar et al., 1973; Banker and Engel, 1994). Special care with the differential diagnosis must be taken when biopsy is performed in very young children. In several instances, fibre size disproportion normalized in successive biopsies taken at different ages (Iannaccone et al., 1987).

In the present kindred, the histograms of two available muscle biopsies showed dissimilarity in size of 56.17 and 53.96%, respectively, between type 1 and type 2 fibres. The mean degree of fibre size disproportion reported in CFTD was 41% (range 12–74%) (Clarke and North, 2003). Clarke and North (2003) reviewed the clinical characteristics of CFTD when either 12 or 25% was used as the minimum degree of size disproportion required for diagnosis, and found that size dissimilarity of 25% or greater was associated with a more severe clinical phenotype and lack of improvement. While the expected percentage of type 1 fibres in normal human muscle is about 40% (Johnson et al., 1973), in CFTD there is usually predominance of type 1 fibres (≥55%). In the two biopsies of the present study, type 1 fibres constituted 78.5 and 84.1% of the fibres, respectively. In most reported CFTD cases, type 2A fibres are smaller than type 2B fibres, the latter constituting less than 5% of the fibres or being absent in up to 35% of the cases (Clarke and North, 2003). In case VI-1 of our family, type 2B fibres represented 4.5% of the total. No other histological abnormalities were identified in our patients upon light microscope and ultrastructural examination. In the present family the homogeneity of pathological findings in muscle samples from two affected individuals showing a disproportion in fibre size without additional abnormalities well into adulthood (25 and 43 years of age, respectively, at the time of biopsy) allows the exclusion of other conditions and suggests this is a distinct nosological entity.

The disorder in our patients fulfils the histopathological criteria accepted for CFTD and the clinical manifestations are reminiscent of those associated with CFTD (Brooke, 1973; Glick et al., 1984; Clarke and North, 2003). Some peculiarities, however, should be noted in our patients. Although CFTD patients are often hypotonic infants (Caille et al., 1971; Argov et al., 1984; Clarke and North, 2003), only rarely were affected individuals in the present family described as floppy at birth. No information on Apgar scores or other parameters upon delivery were available to us. However, interviewed family members generally considered pregnancies, intrauterine movements and deliveries as normal. In contrast to most CFTD cases, with onset of symptoms generally before the first month of age (Clarke and North, 2003), affected members of our family showed the first signs of disease in infancy or early childhood. Respiratory or sucking difficulties in the newborn period were absent in our patients. Motor milestones were not or slightly delayed and weakness was first noticed upon starting to run or climb. A variable clinical picture has been reported previously in CFTD even among members of the same family (Eisler and Wilson, 1978; Clancy et al., 1980; Kula et al., 1980; Sulaiman et al., 1983). In contrast, the pattern of muscle involvement was fairly consistent in all affected individuals of the present family. Weakness predominated in the proximal limb muscles and foot dorsiflexors were almost constantly affected. DTRs were hypoactive or absent, with invariable preservation of the ankle jerk. Extraocular, bulbar, face and neck muscles were preserved in our patients, while involvement of facial muscles, ophthalmoplegia and bulbar or respiratory muscles have been previously reported in up to 35% of mild or moderate CFTD cases and in up to 70% of severe cases (Clarke and North, 2003). CFTD is frequently regarded as a static muscle disorder, without significant deterioration after early childhood and even improvement with age (Brooke, 1973; Curless and Nelson, 1977; Cavanagh et al., 1979). In our patients, however, there was slow but steady progression of weakness. Although two affected individuals in their ninth decade were severely disabled, lifespan was not shortened in this family and none of the patients was wheelchair-bound. Worsening of the symptoms with pregnancy, reported by female patients of the present family, may also occur in other neuromuscular disorders (Rossi et al., 1985; Rudnik-Schoneborn et al., 1997; Chaudhry et al., 2002). Although CFTD generally carries a benign prognosis, the natural history of this myopathy is variable and weakness may be severe in up to 25% of patients, with recurrent respiratory failure and early death (De Reuck et al., 1977; Carboni et al., 1981; Mizuno and Komiya, 1990; Torres and Moxley, 1992; Clarke and North, 2003). Associated defects common in CFTD were absent in our family, such as a high-arched palate, short stature, hip dislocation, scoliosis, joint laxity, joint contractures and pes cavus. A long face is also a common finding among reported CFTD patients. Cases V-2 and VI-1 of the present kindred had long, thin faces, but
so had individual VI-3, who otherwise showed no signs of muscle disease, whereas all other definitely affected family members examined had a normal face. There were no signs of cardiopathy in this family, as disclosed by clinical examination, ECG and routine chest X-ray. Likewise, cardiac involvement is uncommon in CFTD (Sulaiman et al., 1983; Banwell et al., 1999). Cognitive and social development was normal in our patients, as it is in most cases with a reported diagnosis of CFTD (Sulaiman et al., 1983; Jaffe et al., 1988; Clarke and North, 2003).

Routine laboratory workup of affected individuals disclosed no specific abnormalities, including muscle enzymes. This is consistent with previously reported CFTD cases, in which serum creatine kinase and aldolase have been normal usually or slightly elevated (Eisler and Wilson, 1978; Sulaiman et al., 1983; Gerdes et al., 1994; Clarke and North, 2003). Vestergaard et al. (1995) described two brothers with CFTD and insulin-resistant diabetes mellitus. Fasting blood glucose was normal in our cases. Nerve conduction studies were normal ruling out a peripheral neuropathy. Concentric needle EMG showed unequivocal myopathic changes often associated with abnormal spontaneous activity, more severe in the tibialis anterior muscle. EMG evaluation in published CFTD cases, often not quantitative, showed either no abnormality or signs of myopathy with fibrillation potentials and small polyphasic motor unit potentials (Cavanagh et al., 1979; Rowniska-Marcinska et al., 1991). Fibre density was normal or slightly increased in all muscles. As fibre type disproportion may lead to suspicion of fibre type grouping, this finding indicates a normal concentration of muscle fibres in the motor units, thus ruling out a chronic neurogenic process (Rowniska-Marcinska et al., 1991).

The availability of three successive generations for MRI study allowed us to observe the progression of muscle changes with age. The pattern of muscle involvement was strikingly uniform in the present family. The proximal upper limbs, paraspinal muscles and glutei were affected in all individuals examined. In the lower limbs there was early involvement of the vasti and relative long-term preservation of the rectus femoris, semitendinosum, sartorius and gracilis muscles. Interestingly, the pattern of thigh muscle involvement in our family is similar to that reported by Jungbluth and colleagues in congenital myopathies associated with RYR1 mutations, with selective involvement of vasti and adductor magnus and relative sparing of the rectus femoris, gracilis and adductor longus (Jungbluth et al., 2004a). However, within the lower leg these authors report a relative sparing of the tibialis anterior, which is the most affected muscle in our patients. In an extensive MRI study in nemaline myopathy, two different patterns have been distinguished (Jungbluth et al., 2004b). Muscle involvement in patients with nebulin-related nemaline myopathy was pronounced in the lower leg, especially the tibialis anterior, with sparing of all muscle groups within the thigh in the early stages. On the other hand, patients with mutations in the ACTA1 gene showed more diffuse involvement of the thigh and lower leg, with relative sparing of the gastrocnemii. Our patients are similar to the Nebuline (NEB) group in the early and constant involvement of the ankle dorsiflexors, but similar to the ACTA1 group in that the extensors of the knees were weaker than the flexors. MRI has been proposed as a useful method for the study of congenital myopathies and other neuromuscular disorders (Mercuri et al., 2002). However, to our knowledge there are no published reports of muscle imaging in CFTD.

The pathogenesis of CFTD is unknown. While some authors favour the concept of type 1 fibre atrophy (Kinoshita et al., 1975), other investigators have proposed a maturation delay or hypotrophy of a particular population of muscle fibres (Fardeau et al., 1975; Ricoy and Cabello, 1981, 1985). In the patients described here, the absence of a redundant and folded basal lamina in small fibres may be suggestive of hypotrophy rather than atrophy. A family history of disease has been reported in about 40% of CFTD cases in the literature (Clarke and North, 2003). Most of the original cases reported by Brooke (1973) had a family history suggestive of neuromuscular disease, three of them with a similar disorder in a first-degree relative. The mode of inheritance of CFTD (OMIM No. 255310; Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id = 255310) is not well defined and pedigrees consistent with both an autosomal dominant (Brooke, 1973; Fardeau et al., 1975; Kinoshita et al., 1975; Eisler and Wilson, 1978) and an autosomal recessive (Curliss and Nelson, 1977; Cavanagh et al., 1979; Jaffe et al., 1988) mode of inheritance have been reported. Establishing the inheritance of CFTD may be hampered because of the small size of reported families and mildness of symptoms in some patients. In the present paper we report a large, multigenerational kindred in which the disease is transmitted following an autosomal dominant pattern with high penetrance. Previously published families with a diagnosis of muscle fibre type disproportion and autosomal dominant inheritance are scarce and generally comprise only a few individuals. The clinical characteristics of dominant kindreds are varied, some of them including a history of congenital hypotonia and lack of progression of muscle weakness usually associated with CFTD (Fardeau et al., 1975; Kinoshita et al., 1975). Eisler and Wilson (1978) described two members of a family with slow progression of muscle weakness starting in early childhood and without a history of floppy babies. Muscle biopsy from these patients demonstrated type 1 fibre predominance and the authors suggested that this might be a distinct syndrome.

Recently, missense mutations in the ACTA1 gene have been reported in three unrelated cases of CFTD without a family history of muscle disease (Laing et al., 2004). The three children with mutations in ACTA1 represent severe cases of CFTD with generalized weakness also affecting respiratory muscles. ACTA1 mutations accounted for only 6% of cases in the CFTD series analysed, pointing to genetic heterogeneity in CFTD (Laing et al., 2004). Sequencing of the entire coding region of ACTA1 did not disclose mutations in the present family. This is not surprising, since the phenotype of the
present family is different from the clinical picture described in the CFTD cases with ACTA1 mutations. The possibility of a genetic alteration in introns or regulatory regions of ACTA1, as well as gene large deletions or insertions affecting ACTA1, cannot be ruled out in our patients. The discovery of the genetic defect underlying fibre type disproportion in the present kindred may help clarify the pathogenic pathway leading to this disorder. Gerdes and colleagues reported a patient with congenital fibre type disproportion and a balanced chromosomal translocation t(10;17), suggesting that the translocation breakpoints are candidate regions for a causal gene (Gerdes et al., 1994). The patient described by them is different from our cases in that she also had congenital dislocation of the hips and multiple limb contractures. Another candidate locus resides on chromosome 1p, since some features of the distal short arm of chromosome 1 deletion syndrome overlap with those found in CFTD, including fibre type disproportion on muscle biopsy (Shapira et al., 1997; Slavotinek et al., 1999; Okamoto et al., 2002). Although the molecular defect responsible for the 1p deletion syndrome is unknown, it has been proposed that the SKI proto-oncogene may contribute to some of the phenotypic features (Colmenares et al., 2002; Okamoto et al., 2002). Interestingly, this region harbours the selenoprotein N gene (SEPN1), which has been implicated in multimicrocore myopathy and the rigid-spine syndrome, in which type 1 fibre predominance can sometimes be observed (Ferreiro et al., 2002). However, the SEPN1-associated myopathies known to date have an autosomal recessive inheritance. Other candidate genes in this region may include those encoding agrin (AGRN), a crucial factor in the formation of the neuromuscular junction, the actin family gene ARPM2 and mitofusin 2 (MFN2), which mediates mitochondrial organization and is mutated in the axonal form of Charcot–Marie–Tooth disease. A link has also been suggested between mutations in the insulin receptor gene and the muscle alterations in two patients with CFTD myopathy and insulin resistance (Vorwerk et al., 2002; Klein et al., 1999). The large size of the pedigree reported here offers enough power to pursue linkage analysis in the search for the causal gene.

In conclusion, clinical and pathological features of the pedigree reported here are strikingly homogeneous and support the notion of fibre type disproportion myopathy as a separate entity. Because there have been few large series of CFTD reported in the literature, the present kindred provides a thorough overview of this disorder. Although the characteristics of our patients are reminiscent of other cases with mild or moderate CFTD described in the literature, some peculiarities make this family somewhat different from typical CFTD. Thus, whether the condition in this family represents the same disorder as that usually recognized under the eponym CFTD deserves future investigation. The study of the present kindred at the molecular level should have important implications for a better understanding of the biology of this condition.

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