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Case Report

Congenital Fibre Type Disproportion: More Than a Congenital Myopathy

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Abstract

We report three patients who had shown hypotonia and muscle weakness from early childhood with isolated fibre type disproportion on muscle biopsy (MB), initially diagnosed as having congenital myopathy (CM). The genetic analysis revealed mutations in the Protein-O-Mannose Kinase (POMK) gene in patient 1, the D Myotonin-Protein Kinase (DMPK) gene in patient 2 and the collagen 13A (COL13A) gene in patient 3, confirming respectively the diagnosis of congenital muscular dystrophy (CMD), type 1 myotonic dystrophy (MD) and autosomal recessive congenital myasthenic syndrome (CMS) type 19. Reconsidering the diagnosis allowed us to propose a treatment for one patient, to look for cardiac complications in one patient and to establish genetic counselling for all patient's family members. We emphasize throw these observations that congenital fibre type disproportion (CFTD) is a nonspecific histological pattern which could be associated to various types of dystrophic and non-dystrophic muscle disorders, and we discuss its place among the spectrum of CM.

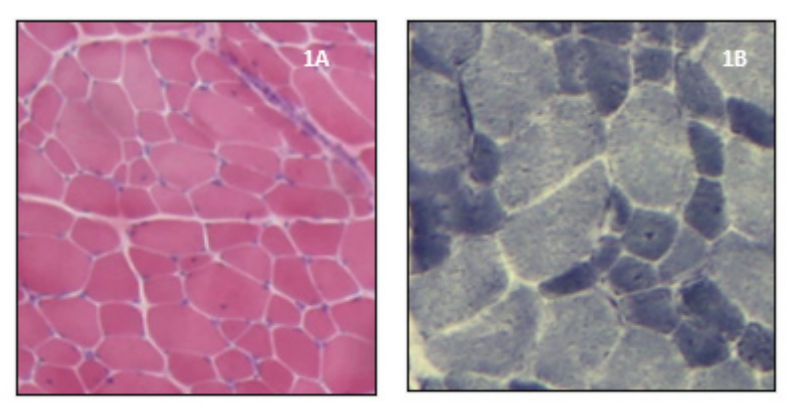
Keywords: Congenital myopathy; congenital fibre type disproportion; gene; mutation

Introduction

CFTD is a histological entity characterized by type 1 fibres smaller by at least 12% than type 2 fibres, and absence of other pathological features on MB [1]. Clinical manifestations are non-specific, there is also no known specific genetic marker or distinct pattern of inheritance [2]. CFTD has been recognized for decades as a subtype of CM. Mutations of the α-tropomyosin slow (TPM3) gene are the most frequently associated with aetiology [3]. In the last years, several reports have subsequently documented cases of CFTD associated with various types of diseases including limb girdle muscular dystrophy (LGMD), CMD, MD and CMS. These findings suggested that CFTD may represent a larger spectrum of disorders [4]. We report phenotype and genotype description of three patients who had shown muscle weakness from early childhood and typical pattern of CFTD on MB allowing to retain initially the diagnosis of CM. The genetic analysis revealed new genes in relation with other types of myopathies.

Patient 1

The patient is an 8-year-old girl with a familial history of first-degree consanguineous parents, 2 similar cases in cousins, severe neonatal hypotonia and respiratory impairment with delayed motor and speech development. At examination she had weakness in the proximal extremities. Serum-creatine kinase (CK) plasma level was elevated, and the electromyogram electromyography (EMG) showed a myopathic pattern. Brain MRI was normal. MB concluded to a CFTD (Figures 1A&1B). The Whole Exome Sequencing (WES) revealed a missense homozygous mutation in the POMK gene, confirming the diagnosis of CMD.

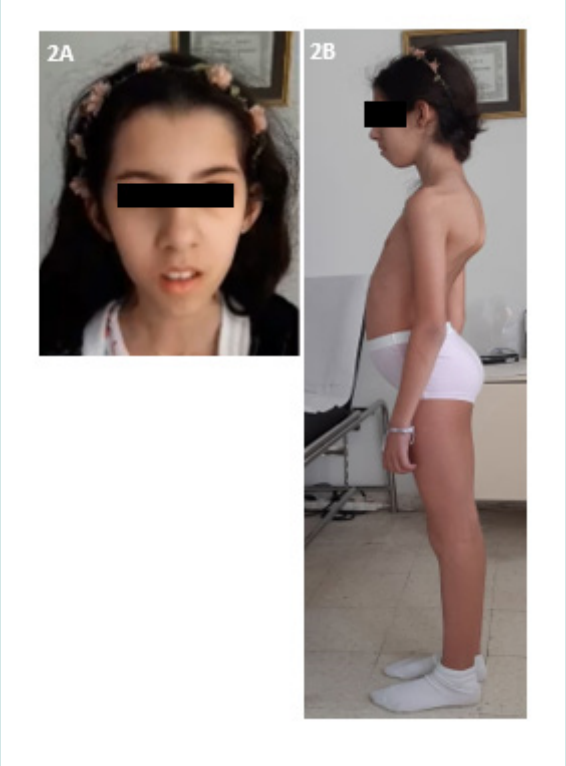


On Hematoxylin and Eosin (H&E) stain (Figure 1A) there are few central nuclei, no necrosis, and no increase of connective tissue. On nicotinamide adenine dinucleotide tetrazolium reductase oxidative enzymatic (NADH) stain (Figure 1B) there is a predominance of type 1 fibres which are significantly smaller than type 2.

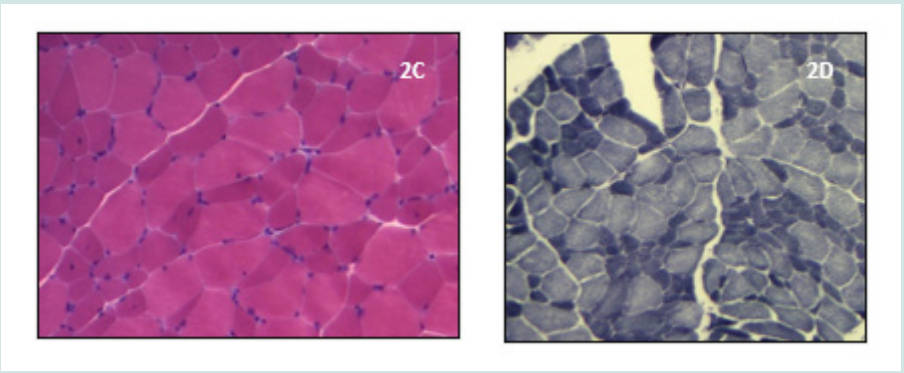
Figure 1: Histopathological features of patient 1.

Patient 2

The patient was born of non-complicated twin pregnancy, had delayed speech development, major learning problems and excessive slowness of movement. On the first examination she was12 years-old, showed a slim phenotype, lordotic stance, facial involvement with ptosis, dysphonia, and moderate proximal-predominant limb muscle weakness (Figures 2A&2B). On MB we found non-specific myogenic changes with variation in fibre size without any dystrophic signs, and a selective atrophy of type 1 fibres (Figures 2C&2D). CK levels were slightly increased. EMG revealed myotonic discharges. This sign prompted the analysis of the DMPK gene allowing the diagnosis of type 1 MD, with 61 expanded CTG repeats.



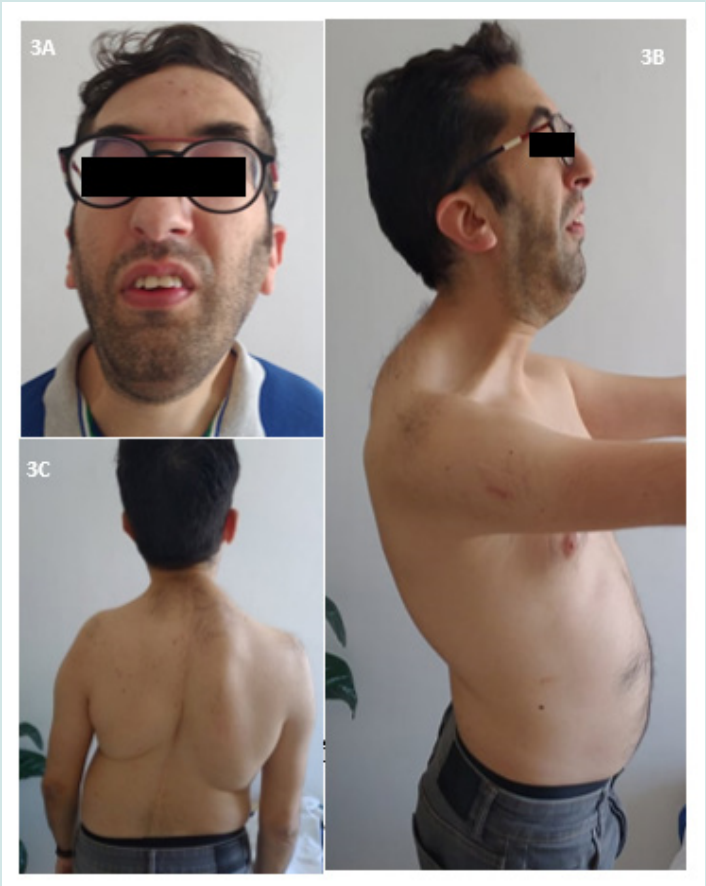
Images of patient 2: A marked atrophy of the temporal, masseter, and sternocleidomastoid muscle (Figure 2A), a slim phenotype with lordotic stance (Figure 2B).



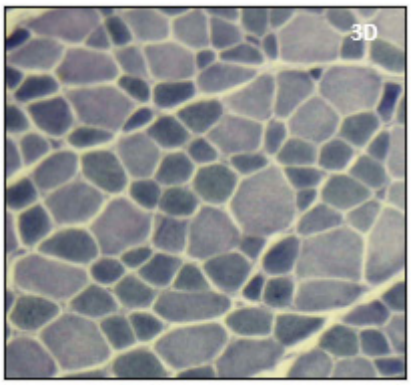
On H&E stain (Figure 2C) there is varied muscle fibre size, few central nuclei, and no increase of connective tissue. On NADH stain (Figure 2D) there is a selective atrophy with predominance of type 1 fibres.
Figure 2: Histopathological features of patient 2.

Patient 3

The patient had a history of congenital hypotonia with delayed motor development. He reported a progressive course of muscle weakness. At the age of 14 he underwent scoliosis surgery, and a non-invasive nocturnal ventilation was recently indicated due to a severe sleep apnea. At time of first examination, he was 34 years old, was still able to walk and had severe weakness of facial, axial, and proximal limbs (Figures 3A-3C). EMG was myogenic, CK levels were normal. MB concluded to CFTD (Figure 3D). The WES allowed the identification of a homozygous mutation in the COL13A gene, confirming the diagnosis of the autosomal recessive CMS type 19. He was treated with pyridostigmine and salbutamol with progressive improvement of his state.



Images of patient 3: A severe fatigable weakness of facial muscles (Figure 3A), scoliosis (Figure 3B), proximal limb weakness with lordotic stance (Figure 3C).



On NADH stain (Figure 3D) there is a selective atrophy with predominance of type 1 fibres.
Figure 3: Histopathological features of patient 3.

Discussion

The core histologic feature that defines CFTD is the selective atrophy of type 1 fibres (slow twitch), with a mean diameter being at least 12% smaller than the diameter of type 2 fibres (fast twitch) on MB. This disproportion must be the main structural pathological change and the diagnosis is often made after ruling out other histopathological findings especially rods, cores, and central nuclei. CFTD is clinically characterized by hypotonia and mild-to-severe generalized muscle weakness at birth or within the first year of life. Multiple joint contractures, scoliosis, long thin face and high arched palate are classic features. Ptosis, facial muscle weakness, ophthalmoplegia and dysphagia were reported in patients with mutations in TPM3, actin alpha 1 skeletal muscle (ACTA1) and ryanodine receptor type 1 (RYR1) genes [5,6]. Intelligence is usually normal, central nervous system abnormalities have been described in some cases [7]. Respiratory involvement is common, reportedly being seen in almost 30% of patients, however cardiac complications are rare [8]. The CK levels are normal or slightly increased. The EMG pattern is not specific, described as normal, myogenic, or neurogenic in reported cases of CFTD [9] The prognosis is often considered to be benign. In a review of Clarke and North of 64 cases, most patients follow a relatively benign course with limb weakness that improves with age. In the same review, 10% of patients died of severe respiratory failure.

To date, 10 genes have been shown to cause CM with CFTD (Table 1). Autosomal recessive, autosomal dominant and X-linked inheritance patterns are known [10,11]. Mutations in the selenoprotein N1 (SEPN1), ACTA1, RYR1 and TPM3 genes are the most frequent causes. There has been a long debate on whether CFTD is a disease entity or if it is 'pathology in search of a disease' [12,13], and this was for several reasons. First, the disproportion of muscle fibres is a feature of almost all subtypes of CM with structural defects, which may constitute a problem of differential diagnosis. In some cases of centronuclear, nemaline or core myopathies, muscle biopsies showed in early stages of the disease an appearance of pure CFTD without other pathological defect. Furthermore, it was demonstrated that histological abnormalities are different in MB taken from the same patient at different ages, or members from different generations of the same family, suggesting that CFTD can be a transient pattern [14-16]. Second, in addition to CM, various neuromuscular disorders in which histological aspect of CFTD is prominent were reported. The use of WES techniques allowed the identification of new genes, broadening the phenotype and genotype spectrum of this entity.

Table 1: Congenital fiber type disproportion: genetic causes and proteins [2, 3, 26-30].

Protein	Gene	Inheritance
Slow α-tropomyosin	TPM3 (25-40%)	AD
Ryanodine receptor 1	RYR1 (20%)	AR
α-skeletal actin	ACTA1 (5%)	AD
β-tropomyosin	TPM2	AD
Selenoprotein	SEPN1	AR
Myosin light chain 2	MYL2	AR
3-hydroxyacyl-CoA dehydratase 1	HACD1	AR
Slow skeletal β-cardiac myosin	MYH7	AD

Titin	TTN	AR
Sodium channel α-subunit	SCN4A	AR

TPM3: Slow α-tropomyosin; RYR1: ryanodine receptor 1; ACTA1: α-skeletal actin; TPM2: β-tropomyosin; SEPN1: selenoprotein 1; MYL2: myosin light chain 2; HACD1: 3-hydroxyacyl-CoA dehydratase 1; MYH7: slow skeletal β-cardiac myosin; TTN: titin; SCN4A: sodium channel α-subunit. AD: autosomal dominant; AR: autosomal recessive.

Cases of muscular dystrophy including Ulrich CMD [17], calpain LGMD [18] and laminopathies [19] were reported. For these reasons, CFTD is becoming a more and more nosologically questionable entity. In fact, among all types of CM, only core diseases, nemaline myopathy and centronuclear myopathy are firmly established as distinct entities [20]. In contrary, spheroid body, reducing body, sarcotubular, predominance of type 1 fibres and CFTD myopathies are not well delineated entities, and their place among subtypes of CM remains uncertain There was widespread concern that these entities are too nonspecific to be of clinical use [21,22]. In our patients, the neonatal onset of symptoms, myogenic pattern on EMG and isolated pattern of CFTD on MB led us to retain the initial diagnosis of CM. The clinical phenotypes were not homogenous, but similar to the features of CM with CFTD. Patient 1 high CK levels (more than five times the upper normal value) and the progressive evolution of patient 3 were atypical for a CM. Results of the genetic analysis excluded the diagnosis of CM and allowed patients to be reclassified to other diagnosis. To our knowledge mutations of POMK1 and COL13A genes were never reported with histological pattern of CFTD. CMD can show CFTD pathology.

In his case series of 10 MB from 8 patients with genetically proven Ulrich CMD, Schessel, et al. highlights the presence of pattern of CFTD and absence of dystrophic changes especially in early stages of the disease. CFTD can also be seen in a MB from patients with congenital MD. Tominaga et al. reported 28 unrelated patients who were pathologically diagnosed as CFTD, 14% of them had marked expansion of trinucleotide (CTG) in the DMPK gene [23]. Histological findings of CTFD were never reported with juvenile onset of congenital MD to our knowledge. Finally, type 1 fibre predominance and disproportion have been rarely noted cases with CMS, with a single genetically analyzed family having mutation of the DPAGT1 gene (UDP-N-acetylglucosamine-dolichyl-phosphate N acetylglucosaminephosphotransferase 1) [24,25]. In our last patient, the second MB, done 30 years after the first, revealed a typical pattern of CFTD. Searching for precise genetic diagnosis allowed us to propose a treatment for patient 3 (diagnosed with autosomal recessive CMS type 19) who received until the age of 34 only supportive treatment. It also motivates us to look for specific cardiac complications in patient 2 (diagnosed with a juvenile form of MD type1) and to establish genetic counselling for his family members.

Conclusion

CFTD remains a controversial entity more and more documented as a histological pattern across various subtypes of myopathies. In our opinion, and after studying the three reported cases, we think that it is better to consider CFTD as a syndrome rather than a formal diagnosis. As the WES analysis becomes more available and the identification of the genetic basis of patients with CFTD is becoming significantly easier, this fact should be motivating for the clinician to look for the precise diagnosis beyond the spectrum of CM. We insist through these observations that we must keep in mind that CFTD can reveal potential treatable or life-threatening diseases.

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Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this publication.

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