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# Muscle Fiber Type Disproportion with an Autosomal Dominant Inheritance

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## Abstract

Congenital muscle fiber type disproportion (CFTD) has been described as a form of congenital myopathy characterized by the smallness and marked predominance of type 1 fibers in a muscle biopsy. Clinical manifestations include hypotonia, nonprogressive muscle weakness, joint contractures, and skeletal deformities. However, it has also been noted that the same pathologic alterations appeared in clinically diverse conditions. Recently, we experienced a family, a mother and two children, in which a muscle biopsy showed the mother to have muscle fiber type disproportion. This case was unusual in that there was a significant progression of weakness, an absence of neonatal hypotonia, and other commonly associated musculo-skeletal deformities. In this report, we describe the clinicopathologic features of the family with a brief review about muscle fiber type disproportion.

Key Words: Congenital myopathy, muscle fiber type disproportion, muscle biopsy

## INTRODUCTION

In 1973, Brooke coined the term "congenital fiber type disproportion (CFTD)" to diagnose a hypotonic child whose biopsy demonstrated an excessive disparity in size between type 1 and type 2 fibers in the absence of other obvious histologic abnormalities.[1] Since then, similar observations have been reported.[2-6] However, other authors have asserted that muscle fiber type disproportion is present in other diseases. Their findings shed light on the possibility that muscle fiber type disproportion is not a disease unique in itself, but is rather associated with a heterogeneous group of muscle diseases and conditions unrelated to muscle diseases.[7-9] At present, it is best to regard the disproportion in muscle fiber size with type 1 smallness with the possibility of being a pathologic pattern that occurs in congenital myopathy under the name of CFTD, as well as occurring in other diseases and conditions.

A majority of CFTD cases follow a relatively uniform pattern characterized by hypotonia and stationary weakness beginning at birth. Here we describe a family, a mother and two children, where muscle tissue obtained from the mother showed muscle fiber type disproportion. Each member of the family showed progressive muscle weakness, which makes this case unique from general CFTD cases.

## CASE REPORT

### Case 1

A 5-year-old girl presented with a waddling gait and showed difficulty in rising from sitting and squatting positions. She was born at term by cesarean section due to her mother's narrow birth canal. Early developmental milestones were unremarkable and she started walking at the age of 12 months. Shortly after that time, her parents noted a weakness, especially when she tried to climb stairs or to run. The weakness was slowly progressive and was expressed by a waddling gait and difficulty in rising from sitting. Intelligence and speech were normal. There was no evidence of scoliosis or other skeletal abnormalities

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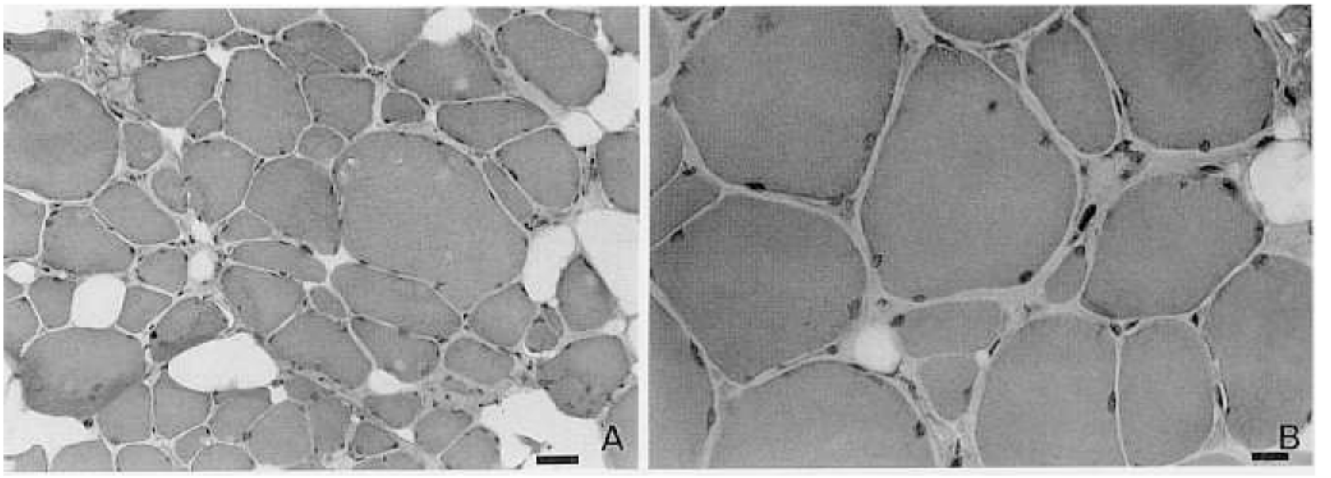


*Fig. 1. H-E staining showing variation in fiber sizes and mild fatty tissue infiltrations (A: ×200, Bar=20 μm, B: ×400, Bar=10 μm).*

except for pes cavus deformity. Muscle bulk was normal and deep tendon reflexes were preserved. The serum creatine kinase (CK) level was 650 IU/L (normal; 35−200). Nerve conduction and needle electromyography studies showed no specific abnormalities.

### Case 2

A 3-year-old boy, the younger brother of case 1, showed difficulty in rising from a squatting position. He was born after an uncomplicated pregnancy by elective cesarean section and had normal developmental milestones. At 12 months, he was able to walk unassisted, but had to crawl some support to first pull himself erect from the floor and proceed with a waddling gait. Upon examination, a mild proximal muscle weakness of the lower extremities and pes cavus deformity were noted. The serum CK was 580 IU/L.

### Case 3

A 33-year-old female, the mother of the children described above, was born normally of an uncomplicated pregnancy. She showed no evidence of any disorder until early childhood when her parents noted that she was weaker than other children. Since that time, she has had very slowly progressive difficulty in rising from a sitting position, climbing stairs, and running. However, since her weakness had not compromised her daily life much, she was not medically assessed until this visit. Upon examination, no abnormality was found in her mental status, cranial nerve function, sensation, or coordination. Pes cavus deformity was found with tight heel cords bilaterally. The weakness was marked in proximal leg muscles and moderate in proximal arm muscles. There were no facial or extraocular muscles weaknesses and the deep tendon reflexes were preserved. The serum CK and nerve conduction studies were normal. A needle electromyography study showed a combination of small brief motor unit action potentials and large motor unit action potentials with reduced recruitment.

### Muscle biopsy

Muscle tissue obtained from the left biceps brachii in case 3 was processed for cryostat-sections. Sections of the muscle (8 μm thick) were studied with hematoxylin-eosin (H-E), modified Gomori trichrome, adenosine triphosphatase (ATPase, at pH 9.4, 4.6, and 4.3), and nicotinamide adenine dinucleotide (NADH)-tetrazolium reductase (TR) stain. There were mild fiber-size variations consisting of many small fibers and a few large fibers with minimal fatty tissue infiltrations (Fig. 1).

Histochemically, the majority of muscle fibers were type 1 (95%) which were smaller than type 2 fibers (Fig. 2, 3). The mean diameter of a type 1 fiber was 42.7 μm and the mean diameter of a type 2 fiber was 64.9 μm. There was no evidence of central cores, minicores, central nuclei, nemaline bodies, reducing

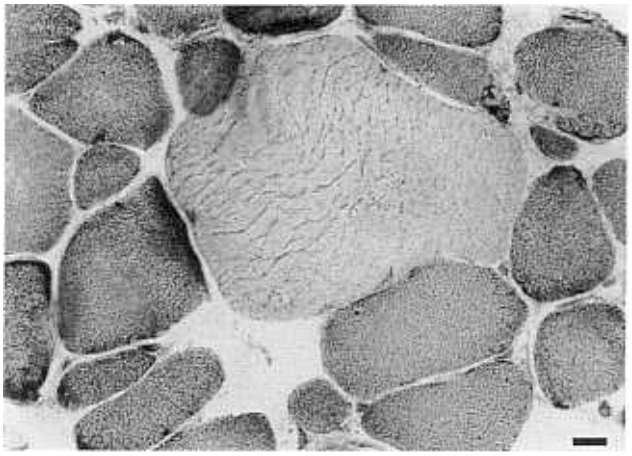

*Fig. 2. NADH-TR stain. Type 1 (dark) fibers are uniformly smaller and more numerous than those of type 2 (×400, Bar=10 μm).*

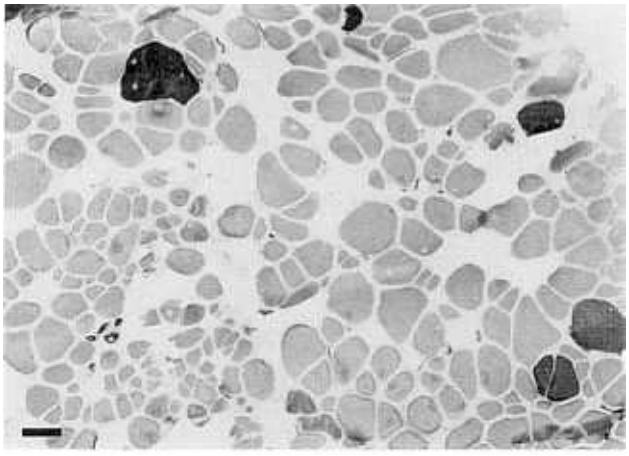

*Fig. 3. ATPase stain (pH 9.4) showing a few type 2 fibers (dark), type 1 fiber (pale) predominance, and relatively small type 1 fibers (×100, Bar=50 μm).*

bodies, target fibers, ragged red fibers, or specific metabolic accumulations. These findings were consistent with muscle fiber type disproportion.

## DISCUSSION

Congenital muscle fiber type disproportion (CFTD) was defined by Brooke as a congenital myopathy. The condition was diagnosed on the basis of a histochemical comparison of the diameters of type 1 and type 2 muscle fibers, with type 1 fibers being increased in number and smaller than type 2 fibers by a margin of more than 12%.[1] Since then, most reported cases of CFTD have generally demonstrated that affected individuals show a very similar clinical presentation. However, it has been noted that the same pathological alterations appeared in diverse conditions such as congenital muscular dystrophy, myotubular myopathy, nemaline myopathy, infantile acid maltase deficiency, infantile myotonic dystrophy, cerebellar hypoplasia, and Krabbe's disease.[3,7-13] The question as to whether this disparity in size between type 1 and type 2 fibers and type 1 predominance should be regarded as a nonspecific epiphenomenon in various congenital myopathies or whether they constitute a distinct disease entity has yet to be answered.

In our cases, three members of a family demonstrated slowly progressing proximal muscle weaknesses, with muscle fiber type disproportion found in one patient. The absence of nemaline rods in a muscle biopsy ruled out the possibility of nemaline myopathy. The patients could not be said to have had infantile myotonic dystrophy because none of them showed clinical myotonia or myotonic discharges in a needle electromyography. Considering the clinical, electrophysiological, and morphological findings, our cases lacked distinctive features supporting the diagnoses of myotubular myopathy, congenital muscular dystrophy, infantile acid maltase deficiency, and Krabbe's disease. We excluded the diagnosis of cerebellar hypoplasia on clinical grounds.

Clinically, CFTD as a congenital myopathy is uniform in its presentation. Congenital nonprogressive hypotonia and weakness, contractures, kyposcoliosis, high arched palate, dislocated hips, short stature, reduced muscle bulk, poor weight gain, and feet deformities are present in different combinations. Intelligence is usually normal. The prognosis is generally known to be good, however, there is no guarantee since deaths have occurred and associated defects are common. The muscles involved may include those of the legs, arms, trunk, neck or face, but pharyngeal and ocular groups are spared. Despite normal sensation, deep tendon reflexes are usually diminished or absent. The serum CK may be normal or slightly elevated.

The question of the inheritance of CFTD has not been completely resolved. Many cases have seemed to be sporadic. Some have been consistent with autosomal dominant inheritance,[14,15] with recessive inheritance also having been suggested in a few reports.[16]

In our cases, even though a muscle biopsy had been processed in only one member (the mother), very similar clinical and laboratory findings suggested autosomal dominance inheritance. Electromyographic changes have been different in reported cases of CFTD. In some cases, the electromyography has been described as normal or myopathic, but not conclusively diagnostic.[3] Other patients have shown reduced interference patterns, complex motor unit action potentials of high amplitudes and prolonged durations, as well as occasional fibrillations favoring a neurogenic lesion.[2,15] The neurogenic electromyographic findings in our case and those from other reports may arise in part from relative fiber type grouping of type 1 fibers and a wide scattering of a few type 2 fibers.

Interestingly, our cases showed a slowly progressive weakness from early childhood, but none of them were characterized as a floppy infant. In addition, a muscle biopsy revealed fatty tissue infiltration and an elevated serum CK was noted. To our knowledge, there is only one report similar to this family.[14] The family described by Eisler and Wilson also had slowly progressing proximal weaknesses starting from early childhood and an elevated serum CK without a history of hypotonia in infancy or other congenital deformities. Their muscle biopsy specimens showed predominance of type 1 fibers and enlarged type 2 fibers. A muscle specimen from one member who had the most marked physical findings showed an increase in connective tissues, degenerated fibers, and minimal inflammatory cell infiltrates. Their genetic features were consistent with an autosomal dominant mode of inheritance. The clinical course of our cases and the family reported by Eisler and Wilson was slowly progressive and was not appropriate to the diagnosis of congenital myopathy. Thus, these conditions could be a rather unique disorder showing type 1 muscle fiber disproportion and predominance, with an autosomal dominant inheritance.

From our experience of these 3 cases and a review of other reports, we suggest that muscle fiber type disproportion is a histological finding and includes heterogeneous clinical entities such as congenital non-progressive myopathy of a hypotonic infant and slowly progressive myopathy of autosomal dominance inheritance.

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