A Case of Congenital Fiber Type Disproportion with Multiple Anomalies

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= 국문요약 =

 복합 기형을 동반한 Congenital Fiber Type Disproportion 1례

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Congenital fiber type disproportion (CFTD)은 근긴장도 저하, 발달 지연, 관절 구축, 골격적 이상 등의 임상 증상을 나타내는 선천성 근육질환으로 근육 조직 조건에서 1형 근섬유의 크기 감소와 수적 증가를 특징으로 하는데 1형 근섬유가 2형 근섬유보다 지름이 12% 이상 작아야 한다. 본 저작은 근긴장도 저하, 발달 지연, 정신 지체, 신생아 간질 발작, 장복양어, 고관절 불완전탈구, 발목관절 구축, 미만성 뇌매, 시신경 위축 등의 소견을 보이며 근육조직 검사에서 확인된 CFTD 1례를 경험하였기에 이를 보고하고자 한다.

Key Words: Congenital fiber type disproportion (CFTD), Congenital myopathy, Mental retardation, Seizure

Introduction

Congenital fiber type disproportion (CFTD) is a rare form of congenital myopathy characterized by the smallness and marked predominance of type 1 fibers and which presents as congenital hypotonia, delayed motor milestones, joint contracture, and skeletal deformities. Muscle biopsy reveals the type 1 fibers are more than 12% smaller than the type 2 fibers in seizes. The term has been used to describe the histological pattern, resulting in confusion about the clinical features of CFTD.

date, our understanding of CFTD has been hampered by the lack of large case series and general consensus on diagnostic criteria. Here we describe a 24-month-old boy who presented with muscle hypotonia, delayed motor milestones, mental retardation with generalized tonic clonic seizure, and pathologic findings of CFTD. Additional findings included left cryptorchidism, congenital subluxation of hip, contracture of ankle joint, diffuse brain atrophy, and optic nerve atrophy.

Case Report

A 2-year-old boy presented with progressive muscle weakness, hypotonia, generalized tonic clonic seizure and delayed psychomotor
milestones. He was born at 37 weeks with birth weight of 2,460 g due to his mothers pregnancy induced hypertension. The Apgar score was 9 at 1 min and he had no perinatal problem. At the age of 12 months, he was hospitalized due to feeding difficulties and abnormal movements such like head dropping and arm extension associated with regurgitation of meals at supine position since 5 months of age. Neither clinical nor electrographic seizure activities are noted on 24 hour video monitoring during the hospital stay. His abnormal movement disappeared after introducing H2 antagonist and metoclopramide. His head circumference and weight were below the 5th percentile. Height was around the 25th percentile. He showed no dysmorphic feature such as long face or high arched palate. His deep tendon reflexes were decreased and he had no Babinski response. Mental milestones were abnormal. He obtained head control at 3 months, creeping at 7 months, sitting with arm support at 10 months, but could not crawl and no sit by himself yet. His verbal speech was limited by two to three words and his eyes could not follow objects. Deterioration of motor and mental function was more rapidly progressed after onset of seizure at 13 months. He also showed left cryptorchidism, congenital subluxation of hip, contracture of ankle joint and optic nerve atrophy.

He had a normal male karyotype. Serum CK level, metabolic tests including serum/CSF lactate and pyruvate, urine organic acid and serum aminoacids/long chain fatty acid results were not specific. At the age of 13 months, asymmetric slowing on left side of brain and frequent sharp wave discharges from right frontal area were noted on EEG. Brain MRI revealed only diffuse atrophy of brain with passive dilatation of ventricles at 18 months of age (Fig. 1). Since he had profound psycho-motor retardation, unexplained diffuse brain atrophy on MRI, and abnormal EEG, we performed muscle biopsy to find the cause of his illness.

Muscle tissue was obtained from left rectus femoris muscle at 2 years of age. Sections of the muscle (8 μm thick) were stained with hematoxylin–eosin (H–E), modified Gomori trichrome technique, succinate dehydrogenase, adenosine triphosphatase (ATPase, at pH 9.4, 4.6, and 4.3), and nicotinamide adenine dinucleotide (NADH)–tetrazolium reductase (TR) statin. There showed selective type 1 fiber atrophy with type 1 fiber predominance of more than 90% of the myofibers (Fig. 2). The mean diameter of type 1 fibers are more than 12% smaller than type 2 fiber. There were no special findings such as central cores,
minicores, central nuclei, nemaline bodies, reducing bodies, target fibers, ragged red fibers, and specific metabolic accumulation.

**Discussion**

CFTD is a congenital myopathy first delineated by Brooke in 1973\(^4\). The criterion of relative type 1 hypotrophy rather than the mean type 2A or type 2B fiber diameter became the central diagnostic feature of the CFTD. Patients with CFTD shared congenital hypotonia, generalized weakness, failure to thrive, multiple joint contractures, scoliosis, long thin face, and high arched palate. Brooke suggested that CFTD was likely to have a genetic basis. Cases with autosomal dominant or recessive inheritance have been reported\(^6\). However, nobody in the family had symptoms of myopathy in our case.

Since many neuromuscular disorders share fiber size disproportion (FSD) of 12% or greater, they should be considered as differential diagnoses to exclude before making diagnosis of CFTD. It has been shown that while FSD is a feature observed in approximately 7% of pediatric muscle biopsies, only 10 to 20% of those children actually have CFTD\(^7\). In addition, CFTD could accompany many central nervous system dysfunction such as perinatal asphyxia, idiopathic mental retardation, cerebral malformations, or Leigh disease. Many myopathic processes have FSD as an ancillary feature, too. They cannot be distinguished from CFTD by clinical features alone. Diagnosis of these disorders needs their own histological findings. Other authors have used the term secondary fiber size disproportion when FSD occurs in this context\(^8\).

In our case, he was manifested as a floppy infant and demonstrated unexplained progressing hypotonia, and proximal muscle weakness with pathological criteria of FSD>12% and type I fiber predominance >90% in muscle biopsy in the absence of other specific histological abnormalities. These features met the criteria for CFTD by Brooke\(^9\). His clinical features including congenital subluxation of the hip, ankle joint contracture, and foot deformities are the same as other previous cases of CFTD\(^9\). Contractures are usually evident at birth, but in some patients with marked weakness and severely impaired mobility, they can develop in later period. The most commonly affected joints are described to be the ankles\(^8\). Cryptorchidism, short stature and poor weight gain have frequently been reported as clinical characteristics of CFTD\(^9\). These features are similar to clinical characteristics of our case.

The mental milestones of our patient were markedly retarded than those of any previously reported case. To the best of our knowledge, his generalized tonic clonic seizure is rarely
found in CFTD cases. In addition, his brain MRI showed evident cerebral atrophy in the absence of other causes like metabolic or perinatal asphyxia. Though the findings of the case were also reported in congenital muscular dystrophy in terms of structural changes of the central nervous system\textsuperscript{10}, the characteristic histological features such as many degenerating or regenerating fibers, or increased connective tissue of congenital muscular dystrophy were absent in the case\textsuperscript{8}. Nevertheless, mental function in CFTD is usually preserved and our literature search also revealed only a few reports of mental retardation in CFTD cases. Clarke et al reported only two patients (3\%) with intellectual disability after reviewing 117 cases of CFTD\textsuperscript{8}.

Shibita et al\textsuperscript{11} reported a boy with feeding difficulties from early infancy, who required artificial ventilation suffering mental retardation. His first muscle biopsy done at the age of 1 month showed CFTD, but the histologic findings significantly improved on the second biopsy at 1 year of age showing type 1 fiber predominance and characteristic morphologic findings such as the formation of nemalines and cores. Quazi et al\textsuperscript{12} also reported three unrelated boys with marked, central, nonprogressive hypotonia, severe psychomotor retardation, seizures, delayed and disharmonic skeletal maturation, and CFTD.

It still remains unclear whether the seizures affected his mental milestones or not and what the main cause was for his seizure. He may be a case of CFTD with type I predominance associated with seizure, mental retardation, diffuse brain atrophy, left cryptorchidism, optic nerve atrophy, congenital subluxation of hip, and contracure of ankle joint.

Unlike other previous cases, he did not make a significant improvement in both motor and mental development. It needs to be clarified why he did not. Many children with CFTD reported later generally had good prognosis. Apparently the disproportion of diameter is not a permanent feature during the course of CFTD. It has been established that a striking correlation between changes in the degree of FSD over time and changes in disease severity in some cases is likely to exist\textsuperscript{8}. These findings suggest that for an individual patient, the clinical course may in part depend on whether type 1 fiber hypotrophy resolves or progresses over time.

In conclusion, the frequent association of CFTD with other diseases suggests that CFTD may not be a specific myopathy but a histological abnormality due to different pathogenic insults which interfere with the normal growth and maturation of the muscle fibers. CFTD is a congenital myopathy whose diagnosis can be made only by muscle biopsy, rather than a distinct syndrome whose diagnosis can be assumed on the basis of clinical characteristics alone. We believe its pathological pattern could be shared with other conditions. Moreover, we should consider CFTD as the differential diagnosis of early onset myopathies.

Abstract

Congenital fiber type disproportion (CFTD) is a rare form of congenital myopathy characterized by the smallness and the marked predominance of type 1 fibers, which presents congenital hypotonia, delayed motor milestones, joint contractures, and skeletal deformities. The muscle biopsy reveals the type 1 fibers are
more than 12% smaller than the type 2 fibers in size. We describe a 24-month-old boy who presented muscle hypotonia, delayed motor milestones, mental retardation with generalized tonic clonic seizures, and the muscle pathologic findings of CFTD. Additional findings included left cryptorchidism, congenital subluxation of the hip, contractures of ankle joints, diffuse brain atrophy, and optic nerve atrophy. We should consider CFTD as a differential diagnosis of early onset myopathy.

References