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# A boy with multi-minicore disease, a rare case of congenital myopathy in childhood

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## Abstract

**We encountered a boy with multi-minicore disease showing marked funnel chest deformity. Inspiratory retraction accompanied by hypotonic muscle led to the discovery of his disease. A definite diagnosis was made by muscle histologic evaluation characterized by excessive variation in the fiber size within muscle fascicles as well as some centronuclear fibers in addition to specific staining methods for muscle fibers. This type of congenital myopathy is rare in childhoods ; thus, it may sometimes be misdiagnosed as congenital cerebral palsy on a simple physical check. Therefore, muscle biopsy is important for the accurate diagnosis of this disease.**

**Key words : congenital myopathy, minicore, multi-minicore disease**

## Introduction

Multi-minicore disease, also termed multicore myopathy, is a congenital myopathy characterized by numerous minicore structures.[1] In this autosomal recessive disorder, characteristic short cores (minicores) can be visualized in most muscle fibers.[1] Based upon the clinical features, 4 subgroups are recognized : classic, moderate (with hand involvement), antenatal, and ophthalmoplegic. The classic form is most frequent, accounting for approximately 75% of patients. Here, we report a boy with classic multi-minicore disease complicated by severe funnel chest.

## Case presentation

A 10-year-old boy with a birth weight of 4,140 g was assigned to an Apgar score of 6 at 1 minute, but the score at 5 minutes was unknown. Family history was unremarkable. There was no consanguinity.

From the time of birth, his sucking power was weak, and he showed diffuse hypotonia and marked funnel chest deformity. At 1 month after birth, inspiratory muscle strength was weak. Bronchoscopy suggested bronchomalacia. At that time, the funnel chest appeared to cause bronchial compression. Subsequently, he failed to gain weight appropriately, and he repeatedly developed respiratory infection. Surgery to correct the funnel chest was performed at the age of 13 months, eliminating the frequent respiratory infection. As for developmental milestones, the boy could support his head at the age of 8 months, and he could stand at the age of 3 years and 6 months ; motor development was delayed. However, language development showed no delay. He was able to walk, but could not run because of muscle weakness. Furthermore, his performance/language IQ showed slight reduction according to WISC-III criteria.

Physical findings included slight scoliosis and limb muscle atrophy in addition to funnel chest.

The cranial nerves were intact. The tendon reflexes of the lower extremities were symmetrical, and no abnormal reflexes were found. No sensory abnormalities were noted.

The leukocyte count, red blood cell count (RBC), and hemoglobin (Hb) were $6.7 \times 10^3/\mu L$, $4.87 \times 10^6/\mu L$, and 14.0 g/dL, resupectively, indicating neither leukocytosis nor anemia. The

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C-reactive protein (CRP) concentration, 0.12 mg/dL, did not suggest inflammation. Serum creatine phosphokinase (CK), glutamic oxaloacetic transaminase (GOT), and lactic acid dehydrogenase (LDH) concentration were 122, 33, and 179 IU/L, respectively, contradicting myositis. The electrocardiogram gave a normal tracing. Respitory function tests showed normal values. Computed tomography (CT) detected patchy, especially symmetric fatty replacement of left and right femoral and gluteal muscles. A quadriceps muscle biopsy specimen showed excessive variation in the fiber size within muscle fascicles as well as some centronuclear fibers. In most fibers, the order of myofibrils appeared disrupted (Figure 1a). No inflammatory changes, such as lymphocytic infiltration , necrotic fibers, or regenerating fibers were present. Myosin ATPase staining showed a predominance of type 1 fibers, but no type 2B fiber defects were evident (Figure 1b). These findings represented myogenic changes without inflammation. Because a congenital myopathy such as multi-minicore disease was suspected, NADH-tetrazolium reductase staining (NADH-TR) and electron microscopy were carried out on the specimen. NADH-TR staining demonstrated several minicore structures (Figure 1c). Electron microscopy showed a disordered myofibril arrangement (Figure 1d), leading to a diagnosis of multi-minicore disease. Testing for gene abnomalities associated with this disease such as mutations in selenoprotein N1 (SEPN 1) and skeletal muscle ryanodine receptor (RYR1) is presently under consideration.

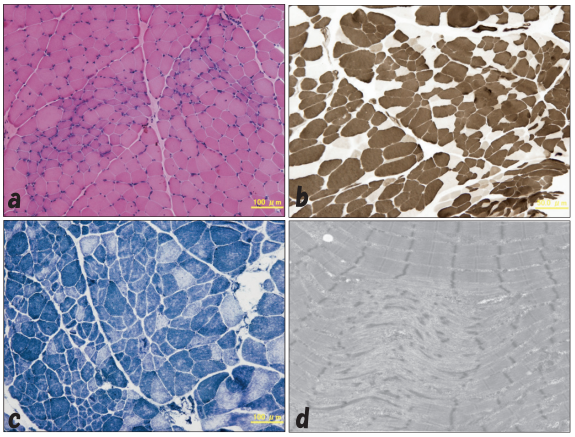


**Fig. 1** Pathologic findings of the biopsied specimens. Muscle fibers differed excessively in diameter, and an irregular myofibril arrangement was observed (a. hematoxylin-eosin, x 100). Type 1 fibers were predominant (b. myosin ATPase, x 100). Minicore structures (c. NADH-TR, x 100) and a disordered myofibril arrangement were noted (d. electron micrograph : original magnification, x 3,000).

## Discussion

Typically, multi-minicore disease clinically develops from the time of birth or during early childhood. Frequently, this disease causes neonatal hypotonia, delayed motor development, or weakness of the proximal and trunk muscles.[2,3] During childhood, skeletal and respiratory abnormalities may occur.[2,3] Nevertheless, funnel chest has not been reported in this disease. Thus, it may be incidental coexsistence, but it may be problematic like our patient having bronchial compression. Scoliosis (mean age at onset ; 8.5 years) and respiratory complications are noted in two-thirds of paitients with the classic form. Respiratory dysfunction often follows cardiac complications such as right-sided heart failure and cardiomyopathy. Classic multi-minicore disease causes varying degrees of spinal rigidity, possibly arising from the contracture of vertebral extensors or restricted spinal flexion. In addition, contracture of the elbows or ankles develops.

The diagnosis of multi-minicore disease requires the confirmation of slowly progressing trunk and proximal muscle weakness and demonstration of multiple minicores in biopsy specimens. The definitive diagnosis is based on the detection of mutations in the *SEPN1*, *RYR1* or *MYH-7* genes. *SEPN1* mutations are detected in 30% of all patients, and in 50% of patients with the classic form.[4] *RYR1* mutations are detected in patients with moderate and ophthalmoplegic forms.[5] Recently, however, other genes such as *MYH-7* gene abnormalities have been identified.[6]

Pathologic findings in this disease include type 1 fiber predominance and the atrophy of muscle fibers. Other light microscopic findings include multiple, irregular minicores related to the loss of mitochondria and endoplasmic reticulum. On electron microscopy, the myofibril arrangement shows scattering within muscle fibers. However, the finding of multi-minicores is not specific to this disease, and a definite pathologic diagnosis may not be possible when clinical findings of congenital myopathy are not marked. In the present patient, symptoms sugges-

tive of congenital myopathy such as hypotonia were observed early in infancy, and a muscle biopsy specimen showed characteristic histologic findings that lead to the diagnosis of multi-minicore disease. With respect to the subtype, this boy was considered to have the classic form, since articular contracture, wrist laxity, and weakness of extraocular muscles were absent. Careful follow-up will be necessary, considering the eventual possibility of cardiac complications.

In summary, we encountered a boy with multi-minicore disease complicated by marked funnel chest. The boy was diagnosed based on the musle histopathologic findings together with the clinical features. However, genetic analysis may eventually be necessary for the definitive diagnosis.

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