

## Central Core Disease – A Case Report –

Ji Hoon Kim · Young S. Park  
Sung-Hye Park · Je G. Chi

Department of Pathology, Seoul National  
University College of Medicine, Seoul,  
Korea

Received : November 14, 2003  
Accepted : January 7, 2004

**Corresponding Author**

Sung-Hye Park, M.D.  
Department of Pathology, Seoul National University  
College of Medicine, 28 Yongon-dong, Chongno-gu,  
Seoul 110-799, Korea  
Tel: 02-740-8278  
Fax: 02-765-5600  
E-mail: shparknp@plaza.snu.ac.kr

Central core disease is a rare autosomal dominantly inherited non-progressive congenital myopathy, which is pathologically characterized by the formation of a "core". We report a 28-year-old female with non-progressive muscle weakness, who had a hypotonic posture at birth. The developmental milestones were delayed with her first walking at 18 months of age. She could not run or walk a long distance and weight-bearing tasks were almost impossible. None of her family members showed motor symptoms. An investigation of the electromyography and nerve conduction velocity showed non-specific results. A gastrocnemius muscle biopsy revealed central cores in approximately 70% of myofibers with a type 1 myofiber predominance and deranged sarcolemmal structures. To the best of our knowledge, this is the fifth report of central core disease in the Korean literature.

**Key Words :** Myopathy, Central Core-Muscle, Skeletal-Ultrastructure

Central core disease is a form of congenital non-progressive myopathy, which was first described by Shy and Magee in 1956. Histologically, central core disease is characterized by central cores that do not react to the phosphorylase and oxidative enzyme. In addition, the checkerboard pattern of the fiber type distribution is replaced by a type 1 fiber predominance. Ultrastructurally, the cores lack mitochondria and most components of the sarcotubular system, and the myofibrillar structure is disorganized in the core regions.

Many cases have been reported throughout the world since 1961, but only four cases have been reported in the Korean literature<sup>1-3</sup>. Central core disease is rare and to the best of our knowledge, this report is the fifth one in the Korean literature.

### CASE REPORT

A 26-year-old female was admitted for a slowly progressive lower extremity weakness. She was born by normal full term spontaneous delivery but suffered some type of dystocia. At birth, she was generally hypotonic and showed a flaccid posture on the

right upper extremity. The symptoms were relieved with the help of rehabilitation exercises. She had no other problems at that time. Her developmental milestones were delayed with her first walking 18 months after birth. Her motor functions were also incomplete. She had to use both arms to sit up or stand and could not run or walk a long distance, and she had difficulties in climbing stairs. The daily living was not particularly difficult but weight-bearing tasks such as carrying heavy materials were almost impossible. Her parents, elderly brother and sister did not show any stigma for a similar muscle disorders.

A physical examination upon admission showed general hypotonia and proximal muscle weakness on both the upper and lower extremities. The weakness was most prominent in hip motions and the lower extremities were weaker than upper extremities. Muscle atrophy was not evident anywhere although her muscle bulk was smaller than that of ordinary persons. Neither fasciculation nor myotonia was detected. There were no sensory changes. The deep tendon reflexes were decreased in the lower extremities. She had no skeletal deformities such as a congenital dislocation of the hips, pes cavus, kyphoscoliosis and finger flexion deformities.

Routine laboratory tests including a complete blood cell count,

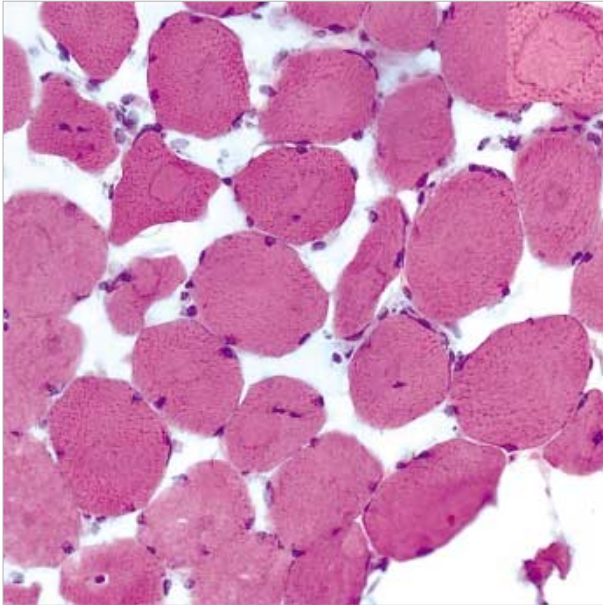


Fig. 1. About 70% of myofibers have central cores, which are stained homogeneously and more brightly in contrast to the surrounding non-core region.

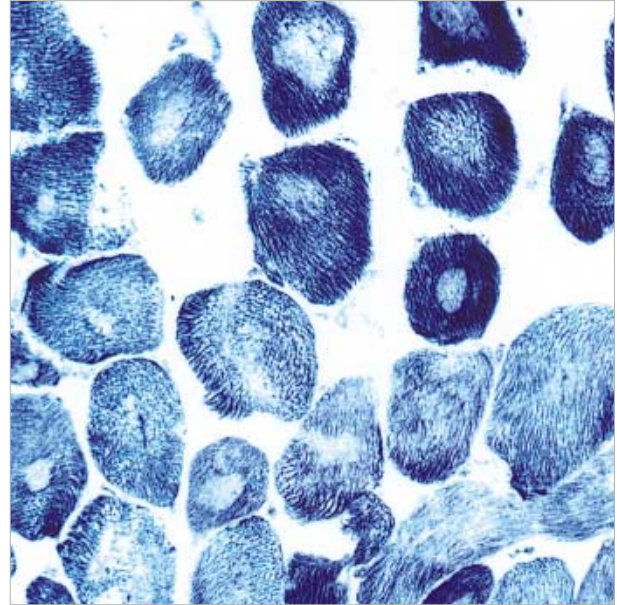


Fig. 2. Sharply demarcated central cores lack mitochondrial enzyme activity (NADH-TR).

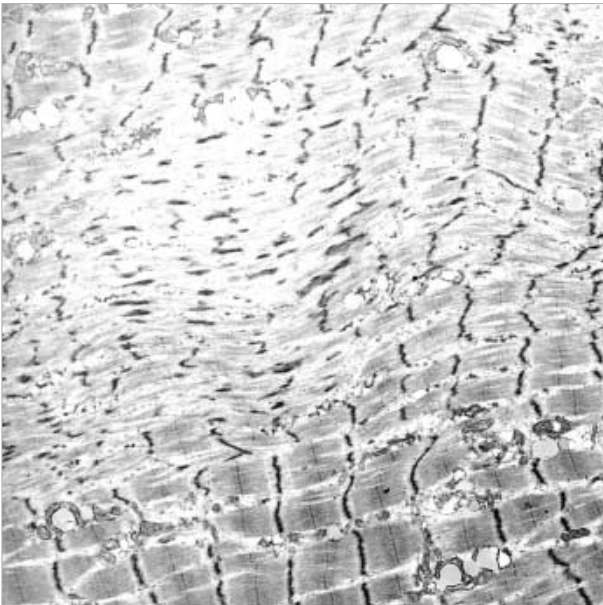


Fig. 3. In the core region, shortening or narrowing of myofibrillar width and disorganization of sarcomeric structures are noted. A structured core is demonstrated in this field ( $\times 4,600$ ).

blood urea nitrogen, creatinine, liver function test panel, serum electrolytes and urinalysis were within the normal limits. The serum creatine phosphokinase (CPK), and lactic dehydrogenase (LDH) levels were not elevated. Electromyography of the left vastus medialis exhibited normal motor unit potentials with the full recruitment and slightly increased polyphasia, which could be

regarded as a normal finding. The nerve conduction velocity was also normal. A left gastrocnemius muscle biopsy was performed under the clinical impression of congenital myopathy or other non-progressive muscular dystrophies.

Fresh muscle specimens were obtained immediately after the biopsy. A portion was snap-frozen, and the others were taken for electron microscopy and routine histology. Serial sections of the frozen tissue with a 10  $\mu\text{m}$  thickness were stained with hematoxylin and eosin, modified Gomori trichrome, and periodic acid-schiff (PAS). Histochemically, the tissue sections were stained with NADH-tetrazolium reductase (TR) and preincubated with ATPase at pH 9.4.

Hematoxylin and the eosin stains of the cross-sectioned myofibers showed a minimal size variation and some internal nuclei. The interfascicular area was moderately widened by the ingrowth of fat tissues. Individual myofibers contained central "cores" that consisted of homogeneous and more brightly stained areas in contrast to the surrounding normal myofibrils. These structures were evident in approximately 70% of myofibers and the area of the cores was estimated to be 30-50 percent of the myofiber's cross-sectional area (Fig. 1). PAS staining also delineated these cores clearly. There were no degenerating or regenerating myofibers. There were neither endomyseal fibrosis nor inflammatory cell infiltration.

Histochemically, the cores showed no or negligible activity on the NADH-TR (Fig. 2). This change was prominent in the type

1 myofibers with a type 1 fiber predominance. Staining for ATPase preincubated in pH 9.4 was not suitable for an evaluation due to the poor tissue preparation.

Ultrastructurally, the core region was generally well demarcated and there was an abrupt transition between the cores and surrounding normal myofibril. The longitudinal section showed that the thickness of the cores was almost 5 to 7 times that of myofibril. Both structured and unstructured cores were present in areas where the mitochondria and sarcotubular system were lost or deranged (Fig. 3). In the structured cores, the myofibrils were closely packed together with a shortening of the sarcomeres and a narrowing of the myofibrillar width. Sarcomeric structures were relatively well-preserved with zig-zagged Z-lines. In the unstructured cores, the sarcomeres were markedly disorganized into thick and thin filaments with irregularly arranged Z-bands, which were reduced to small fragments and took a wavy or curvilinear course. The ultrastructural structures including the mitochondria were within the normal limits in the surrounding non-core region.

## DISCUSSION

Congenital myopathies are similar to one another in several aspects.<sup>4</sup> Generally, a peculiar pattern of inheritance can be defined. Muscular weakness, which is the main clinical manifestation, occurs in early childhood and is mostly non-progressive in nature. The site of involvement tends to be centered in the lower extremities and in the proximal side. Muscle atrophy is not conspicuous although most patients have thin muscles. The deep tendon reflexes are usually decreased or absent. A pathologic examination is warranted in most cases because a definite diagnosis is impossible based on clinical grounds alone, central core disease is a representative example in this aspect.<sup>1-5</sup>

The clinical manifestations of our patient are generally consistent with those of most reported cases, which have been described as a benign and non-progressive course of muscle weakness since birth. The developmental milestones were delayed and the motor function was incomplete as usual.

Pathologically, this case could be discriminated from other congenital myopathies, which can exhibit core-like structures, such as nemaline myopathy and denervation atrophy. Nemaline myopathy with core fibers has subsarcolemmal, intermyofibrillar or intranuclear rod-like structures that are related to the Z-band with a peripheral distribution in the myofibers. However, the coexistence of rods and cores in the same biopsy has occasionally

been reported.<sup>5,6</sup> Denervation atrophy reveals a peripheral loss of myofilaments with relatively preserved core regions in electron microscopy.

Histochemically, NADH-TR staining typically shows a loss or attenuation of the oxidative enzymes in the core region with a type 1 fiber predominance in central core disease, and this feature is true in our case. There appears to be no correlation between the number of muscle fibers containing cores and the severity or progression of the diseases.<sup>4</sup> However, some cases with an adult onset have been reported to have a more severe type 1 fiber predominance than those of an early onset.<sup>7</sup> This patient was a flaccid infant at birth and had exhibited persistent muscle weakness for 26 years. The muscle biopsy result, which showed a prominent type 1 fiber predominance, is compatible with her long-standing history of 26 years, if it is true that the disease progression is reflected in the degree of type 1 fiber predominance.

The mechanism of core formation was previously believed to be neurogenic with regard to the morphologic features and type 1 fiber predilection, which are similar to the targetoid fibers found with a denervation and reinnervation.<sup>8</sup> However, several electromyographic observations and motor innervation studies suggest that the "neurogenic" hypothesis is inconclusive. Another hypothesized cause is the structural alterations in development such as abnormalities of the sarcoplasmic reticulum and T-tubules, which are found as consistently as the depletion of mitochondria,<sup>9</sup> but has not been demonstrated. In some reports, the number of cores increased with the patient's age,<sup>10</sup> but generally, it is unclear at what stage of the disease the cores appear and whether the cores once formed either increase in number or regress with age.

Generally, central core disease is inherited as an autosomal dominant trait although some sporadic cases have been reported. A skeletal muscle biopsy of the family members of this patient was not performed because they were all asymptomatic. Clinically unaffected relatives may have cores or a type 1 fiber predominance in their skeletal muscle biopsy and the identification of sporadic cases requires a negative muscle biopsy of their relatives. Therefore, the inheritance pattern of this case cannot be stated.

Central core disease is known to be related to malignant hyperthermia, and both are disorders of calcium regulation.<sup>11</sup> Most cases of central core disease and approximately half of the malignant hyperthermia cases showed a mutation of the ryanodine receptor gene (RYR1), which encodes the key channel that mediates the release of calcium in response to depolarization of the sarcolemma during excitation-contraction coupling. The RYR1 gene was reported to be harbored in chromosome 19q13.1.<sup>12</sup> A mutation study of the RYR1 gene could not be performed due

to the inability to extract DNA from the paraffin embedded biopsy materials.

Although many cases of central core disease have been reported worldwide, only four cases have been reported in the Korean literature. We report a fifth central core disease patient with the typical clinical and pathological features.

## REFERENCE

1. Myung NH, Suh YL, Chi JG, Hwang YS. Central core disease. -A case report- J Korean Med Sci 1993; 8: 235-40.
2. Han TR, Paik NJ, Lee SJ. A case report of central core disease. J Korean Acad of Rehab Med 1994; 18: 843-8.
3. Go JT, Kim DW, Kim KJ, Go TS, Hwang YS. Three cases of central core disease. J Korean Child Neurol Soc 1993; 1: 186-92.
4. Engel AG, Frazini-Amstrong C. Myology. 2nd ed. New York: McGraw-Hill Inc. 1994; 1487-529.
5. Afifi AK, Smith JW, Zellweger H. Congenital non-progressive myopathy: central core disease and nemaline myopathy in one family. Neurology 1965; 15: 371-81.
6. Bethlem J, Arts WF, Dingemans KP. Common origin of rods, cores, and focal loss of cross-striations. Arch Neurol 1978; 35: 555-66.
7. Patterson VH, Hill TRG, Fletcher PJH, Heron JR. Central core disease: clinical and pathological evidence of progression within a family. Brain 1977; 102: 581-94.
8. De Coster W, De Reuck J, Vander Eecken H. The target phenomenon in human muscle: A comparative light microscopic, histochemical and electron microscopic study. Acta Neuropathol (Berl) 1976; 34: 329-38.
9. Cohen ME, Duffner PK, Heffner R. Central core disease in one of identical twins. J Neurol Neurosurg Psychiatry 1978; 41: 659-63.
10. Dubowitz V, Roy S. Central core disease of muscle: clinical, histochemical and electron microscopic studies of an affected mother and child. Brain 1970; 93: 133-46.
11. Denborough MA, Dennett XK, Anderson RMcD. Central core disease and malignant hyperthermia. Br Med J 1973; 1: 272-3.
12. Haan EA, Freemantle CJ, McCure JA, Friend KL, Mulley JC. Assignment of the gene for central core disease to chromosome 19. Hum Genet 1990; 86: 187-90.