Journal of Korean Medical Science
Vol. 8, No. 3, 235-240 June 1993

Central Core Disease

— A Case Report —

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Central core disease is a rare congenital myopathy characterized by the formation of "cores" that consist of abnormal arrangement of myofibrils inside the myofibers.

We report a 5-year-old Korean girl who showed a fairly typical clinical course of non-progressive muscle weakness. Electrodiagnostic studies showed low-amplitude polyphasic electromyograph and normal nerve conduction velocity. Gastrocnemius muscle biopsy showed central cores in over 80% of the fibers on H&E section. Histochemistry revealed deficient or absent mitochondrial enzyme in the cores and type I predominance. Ultrastructurally both structured and non-structured cores were found separately or simulataneously in one fiber. This case is the first report in the Korean literature.

Key Words: *Congenital myopathy, Muscle, Central core disease, Ultrastructure.*

INTRODUCTION

Central core disease is a form of congenital non-progressive myopathy, originally reported by Shy and Magee in 1956. Histologic sections revealed central cores in most fibers, non-reactive on enzyme stainings for mitochondrial enzymes. Ultrastructurally, the cores represent well demarcated abnormal myofibrillar structures with sarcomeric and band abnormalities. Decreased number or absence of mitochondria and sarcotubular system is another important ultrastructural feature.

Central core disease has not been reported in Korea yet. The disease is very rare and also rather difficult to be diagnosed because histochemistry and electron microscopic examination are necessary for diagnosis. This is the first case report of central core disease in Korea.

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CASE REPORT

A 5-year-old girl was referred in June 1992 to Seoul National University Children's Hospital with delayed motor milestone and walking abnormality. She was born by normal full term spontaneous delivery. Since birth, she had been generally hypotonic and showed delayed motor milestone which included head control at 3 months, sitting alone at 1 year, and first walk at 27 months. Her gait was waddling and she could not walk long distances. Her father and elder brother showed similar findings. They could not run and had difficulty in climbing stairs.

Physical examination of this patient at admission revealed slight lumbar lordosis and equinus deformity of the right foot. She was generally hypotonic and the muscle weakness was more prominent in the lower extremity than the upper. Muscle atrophy was not detected anywhere. Neither fasciculations nor myotonia were noted. Deep tendon reflexes were absent at the ankle and knee joints. Neurological examination did not reveal any abnormality. Routine laboratory data including hemoglobin, white blood cell count, blood urea, total serum protein, serum electrolytes, and routine urinalysis were all within normal limits. Serum creatine phosphokinase (CPK) and lactic dehydrogenase

(LDH) measured 83 IU/l and 254 IU/l, respectively. electromyography of the left vastus medialis and tensor fascia latae revealed short-duration, small-amplitude, polyphasic motor unit potentials, which are consistent with primary myopathy. Nerve conduction study was normal. With the clinical impression of congenital myopathy or cerebral palsy, a muscle biopsy was done from the left gastrocnemius.

PATHOLOGICAL INVESTIGATION

Fresh biopsy specimens were obtained at operation room. A portion was snap-frozen, and the remainders were utilized for electron microscopy and routine histology. Transverse and longitudinal 10μm cryostat sections were stained by hematoxylin and eosin, modified Gomori trichrome, phosphotungstic acid hematoxylin (PTAH) and Masson trichrome. Histochemically the biopsies were stained for ATP-ase preincubated at pH 9.4 and NADH-tetrazolium reductase.

Pathologic Findings.
Histology:

Hematoxylin and eosin stains of cross-sectioned myofibers showed a mild variation in fiber diameter, increased number of centrally-placed nuclei, and ocasionally degenerated fibers. The interfascicular area was midly widened by infiltrated adipose tissue. Most myofibers within each fascicle contained more deeply eosinophilic central "cores" which were fairly distinct and easily distinguishable from the surrounding normal myofibrils (Fig. 1). The volume of the cores in cross-sections was estimated to be 40 to 60 percent. The cores showed no distinct pattern of myofibrillar arrangement. Most involved myofibers contained single central cores. However, peripheral cores or multiple cores were rarely seen. Modified Gomori trichrome preparations delineated these cores more

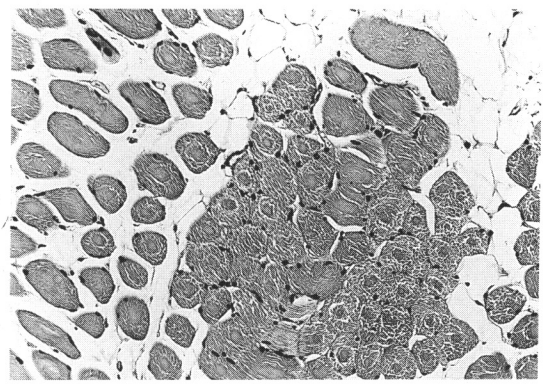

Fig. 1. Most myofibers show well-demarcated central core formations on cross-section (H&E, ×200).

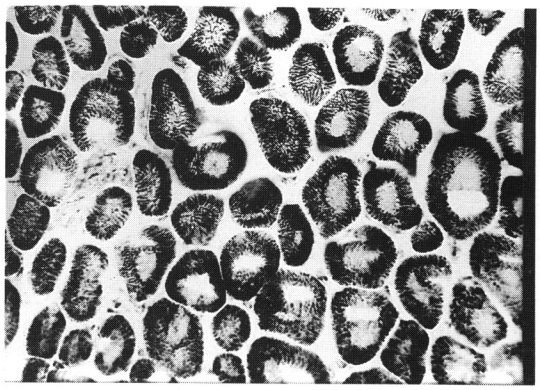

Fig. 2. Unstained central cores with abrupt transition from stained myofibrils are seen on modified Gomori trichrome staining (×400).

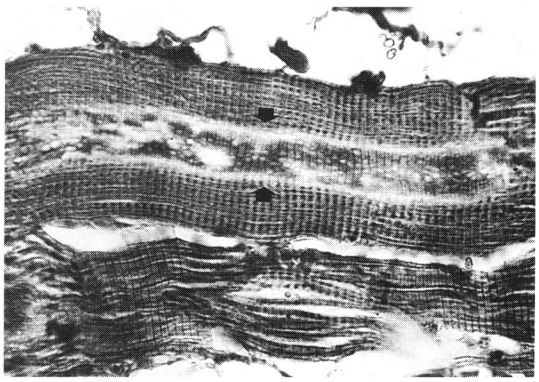

Fig. 3. Longitudinal view of a well-defined central core (arrows) shows central lack of stainability throughout the length of the myofiber (PTAH, ×1,000).

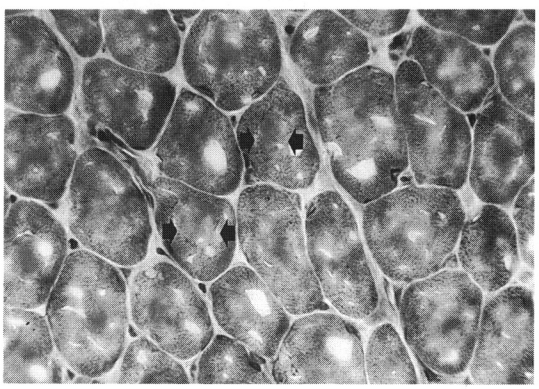

Fig. 4. NADH-TR staining reveals central decreased staining areas in comparison to the peripheral areas (×400).

clearly. The cores were intensely light blue because of deficient mitochondria (Fig. 2). The cores showed weaker or almost no staining than surrounding areas on PTAH and Masson trichrome stainings. The cores were uniform in diameter and extended along the whole length of the fiber that could best be demonstrated on longitudinal sections with PTAH staining (Fig. 3).

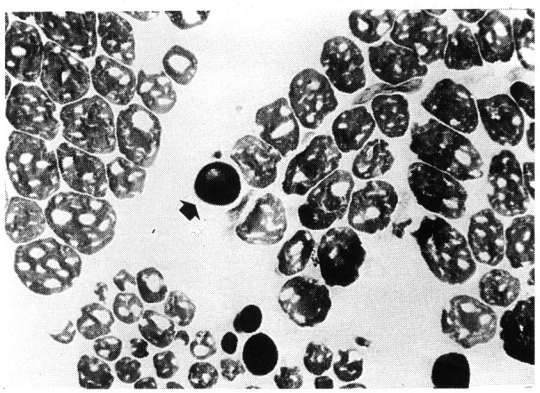

Fig. 5. Only a few darkly stained type II fibers (arrows) are seen, revealing type I fiber predominance on ATPase (pH 9.4) staining (×400).

Histochemical staining:

The cores showed no or negligible activity on NADH-TR. This was true where the cores were multiple or peripherally located (Fig. 4). In addition, at least more than 90 percent of the fibers were type I, indicating significant type I predominance (Fig. 5). The cores were present in about 80 percent of the type 1 fibers but seldom seen in type 2 fibers.

Electron microscopy:

Generally the transition between the core and surrounding regions was abrupt. Both structured and non-structured cores were found. The longitudinal section revealed the cores had the width of 4-6 myofibrils , showing two structured and non-structured pattterns (Fig. 6). Both lesions contained little or no mitochondria and sarcotubular system. In the structured cores, the myofibrils were more closely packed together with shortening of their sarcomeres and fairly well-preserved sarcomeric patterns (Fig. 7). The Z lines were thick and zig-zagged. In the non-structured cores, the sarcomeres were disorganized by thick and

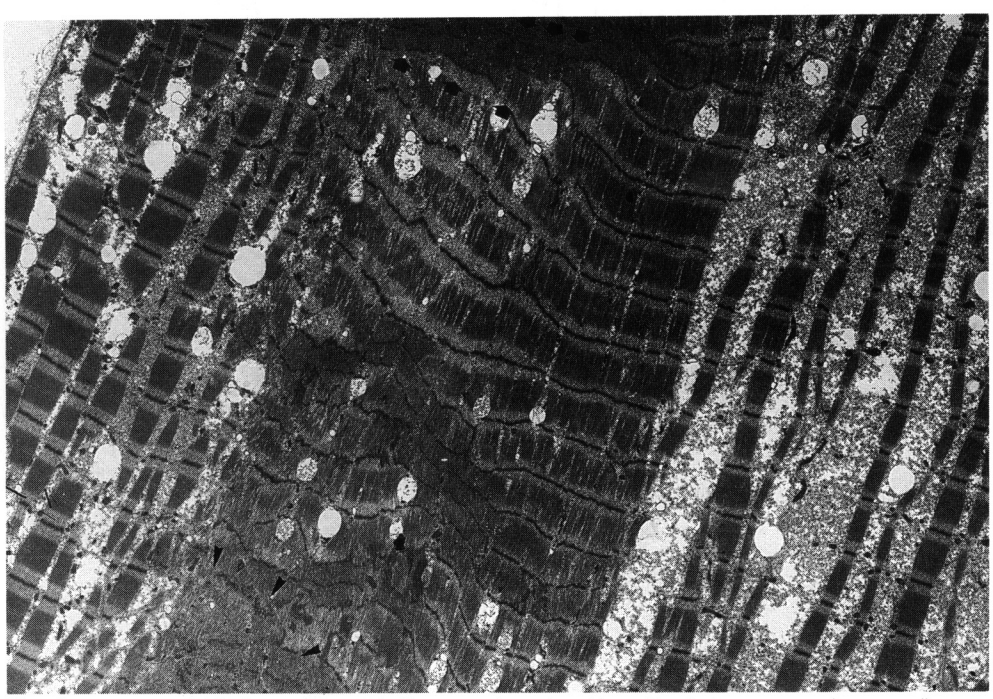

Fig. 6. Ultrastructural findings of a muscle fiber reveal an abrupt transition between normal surrounding myofibrils and abnormal myofibrils of central core. Two structured (arrows) and unstructured (arrowheads) types are noted in the cores (×4,600).

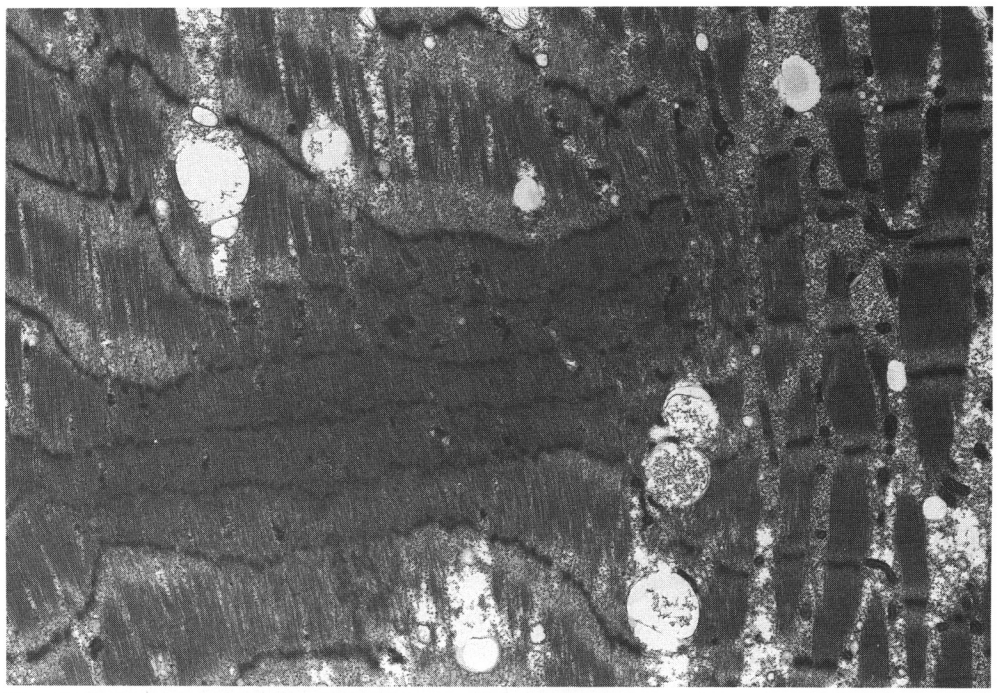

Fig. 7. Structured type of central core reveals shortened tightly packed myofibrils showing well reserved sarcomeric pattern but shortened sarcomeres with irregularly thickened Z-bands (×11,500).

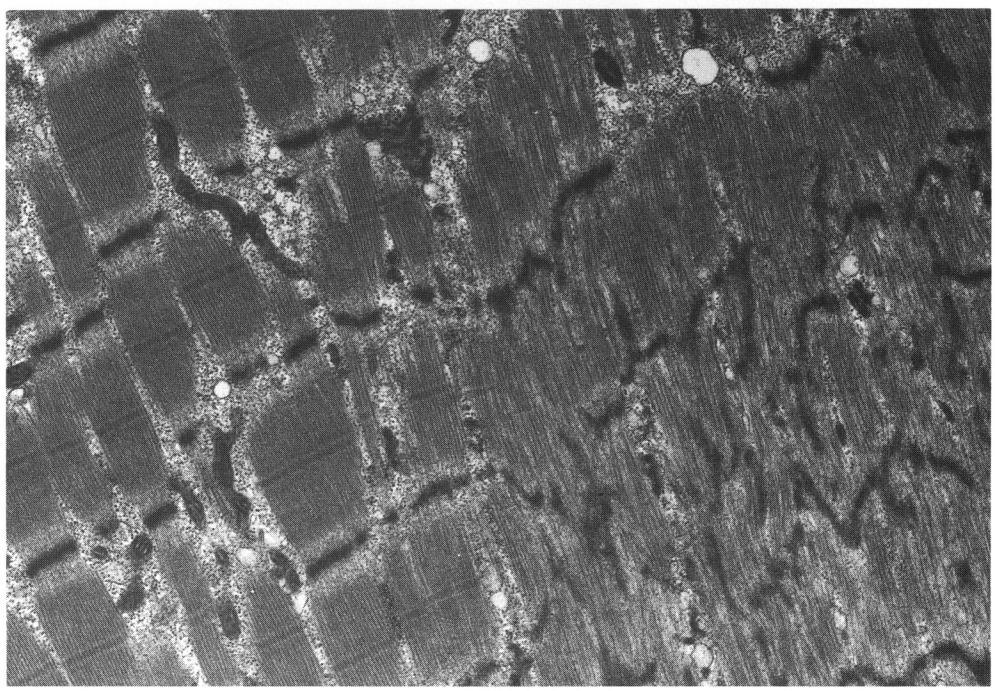

Fig. 8. Non-structured core shows markedly reduced or absent mitochondria and sarcotubular system and characteristic sarcomeric dissolution with wavy curvilinear fragmentation or loss of Z-bands (×18,400).

thin filaments that were moderately reduced in number but retained longitudinal arrangement. The Z bands were either reduced to small fragments or displayed a wavy, curvilinear or angular course (Fig. 8). The interfibrillary space was practically absent and the sarcoplasmic reticulum and mitochondria were markedly diminished. It was interesting to note that these structured and non-structured cores were often present in one fiber closely juxtaposed. Small patches of complete loss of myofibrillar material occurred infrequently. All structures including mitochondria were well preserved in surrounding region.

DISCUSSION

Congenital myopathies possess a number of common characteristics (Engel et al., 1976). In most of cases, a pattern of inheritance has been defined. Muscular weakness, a main clinical manifestation, usually has its onset early in life and symmetrically affects proximal limb muscles. Deep tendon reflexes are usually decreased or absent. The serum creatine kinase is usually not increased. Since these disorders cannot be diagnosed with confidence on clinical grounds alone, muscle biopsy with histochemical and electron microscopic examination is necessary for diagnosis. Among congenital myopathies central core disease is particularly based on morphological alteration.

Our case satisfies the clinical criteria of congenital myopathy, by showing a benign and non-progressive course of muscle weakness since birth, family history and electrodiagnostic studies of the muscle and nerve. Pathologically, routine H&E histology could easily detect "central cores" in most fibers although the distinctness was unequal in individual cores. Approximately 70 to 80 percent of the fibers are thought to have cores of various density. This enabled us to distinguish from other myopathies that can show "core" like structures, such as denervation atrophy or nemaline myopathy. Ultrastructurally denervation atrophy reveals loss of myofilaments in the periphery, and the core itself is relatively preserved. Nemaline myopathy with core fibers reveals rod bodies from abnormal Z-bands mainly in the periphery. Other conditions include reinnervation and tenotomy having a core fiber-like target fiber. Target fibers are regenerated ones and are characterized by consisting of 3 hypo-, hyper-, normo-active enzymic zones, showing segmental involvement, containing single cores, and appearing only at reinnervation.

Cytochemically the reduction of demonstrable oxidative enzymes in the core and the diminution of myofibrillar ATPase is well-known and was also demonstrated in our case. In modified Gomori thichrome stain, the core may be strongly azurophilic or light blue with areas of deeper staining between the fibrils (Gonatas et al., 1965). These tinctorial differences could represent a different stage in the pathologic process (Gonatas et al., 1965). In our case the cores stained light blue and were sharply demarcated from the peripheral myofibrils, suggesting that this case in relatively late stage as she had been ill for 5 years. Histochemical staining for NADH-TR in this case showed a staining defect in the central core, which demonstrated mtochondrial deficiency. ATPase staining preincubated at pH 9.4 revealed that over 90 percent of the fibers were composed of type 1 fiber, which coincides with previously reported cases.

The most outstanding ultrastructural abnormalities in our case were change of sarcomeric system and Z band area within structured and unstructured cores. Two types differ in the degree of ultrastructural changes and there is usually only one type in a fiber. However, our case showed both types within one myofiber, which has not been mentioned in previous case reports and thus appears to be exceptional. The etiology or pathogenesis of the central core disease is not yet clear and has been mentioned by only a few authors (Engel et al., 1976; Engel et al., 1960). The presence of type 1 predominance and similarity to the target fiber suggests neural factors in the etiology but the type predominance may also be generated by changes in structural components during the developmental period (Engel et al., 1976). Speculation on pathogenesis includes developmental abnormality before the time of myofiber differentiation, mitochondrial defect, and focal regional abnormality (Engel et al., 1960).

There appears to be no correlation between the number of muscle fibers containing cores and the severity, progression or clinical manifestations of the disease (Engel et al., 1976). However, some cases with adult onset are reported to have more severe type 1 predominance reinnervated by type 1 axons (Patterson et al., 1979) than cases of early onset, whose clinical maifestation depends on the age of onset and rate of progression of this process. Our case was a floppy infant since birth and had shown persistent muscle weakness for 5 years. The results of muscle biopsy revealed type 1 fiber predominance over 90 percent of fibers with central cores. If it is true that the disease progression is reflected in the degree of type 1 predominance and the cores are seen only in type 1 fibers (Engel et al., 1976), the cores will be increased as the type 1 predominance is more profound and the disease is more advanced.

Worldwide, about 75 cases of central core disease have been reported up to 1987. Thereafter new clinical findings were known to be associated with the disease, which include adult onset, progressive course, and association with malignant hyperthermia, musculoskeletal defect and cardiac abnormalities (Shuaib et al., 1987). Among these our patient revealed the association of a musculoskeletal defect, i.e., the equinus deformity of the right ankle and slight lumbar lordosis. The family history of this patient suggested autosomal dominant inheritance but the biopsy was not done in family members.

Several forms of congenital myopathies such as myotubular myopathy (Chi, 1986) and nemaline myopathy (Suh et al., 1989; Park et al., 1990) have been reported in Korea. However, central core disease has never been described.

REFERENCES

Chi JG. *Myotubular Myopathy (A case report) Korean J Pathol, 20:305-12, 1986.*

Engel AG and Banker BQ: *Myology. Vol II. McGraw-Hill, New York, pp1528-1537, 1976.*

Gonates NK, Perei MC, Shy GM, Evangelista I. Central "core" disease of skeletal muscle: *Ultrastructural and cytochemical observations in two cases. Am J Pathol 47:503-524, 1965.*

Engel WK, Foster JB, Hughes BP, Huxley HE, Mahler R. Central core disease: *An investigation of a rare muscle cell abnormality, Brain 1960. 83, 167-85.*

Park SH, Chi JG, Hwang YS, Choi IH, Moon HR: *Nemaline Myopathy-Enzyme Histohemical and Ultrastructural Study-Seoul J Med 31:183-190, 1990.*

Patterson VH, Hill TRG, Flectcher PJH, Heron JR. Central core disease: *Clinical and pathological evidence of progression within a family brain, 102, 581-94, 1977.*

Shuaib A, Paasuke RT, Brownell KW. Central core disease: *Clinical features in 13 patients Medicine, 66, 389-96.*

Suh CK, Chung JS, Yi SD, Park YC, Chi JG. *A Case of Childhood Nemaline Myopathy. J Korean Med Sci, 32:1126-1130, 1989.*