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Muscle biopsy of a 15-year-old boy with muscle atrophy and weakness of the extremities from infancy

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Key words: central core disease, congenital myopathy, floppy infant, ryanodine receptor gene.

CLINICAL HISTORY

This 15-year-old boy was hospitalized for evaluation of muscle atrophy and weakness of the extremities from infancy. The delivery had been full and uneventful, and his bodyweight at birth was 3250 g. After birth his sucking and crying were weak, and the extremities were floppy.

Muscle atrophy became apparent when he was 8 months old. He began to walk at 2 years and 1 month. After that his physical development was delayed as well but his mental development was normal.

On admission his mental state was normal. He showed slight to moderate muscle atrophy and weakness in the face, neck and his extremities. Deep tendon reflexes were diminished. He could walk but could not run. The sensory systems were unremarkable. Creatine kinase and aldolase were within normal limits. A muscle biopsy was done at the right quadriceps femoris muscle.

MICROSCOPIC FINDINGS

Hematoxylin-eosin-stained sections showed mild variation in the diameter of muscle fibers, ranging from 50 to 90 μm. The center of each muscle fiber was deeply stained with a pale stained halo (Fig. 1a). There were no inflammatory cell infiltrates or collagenous tissue proliferation in the interstitium. Nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR)-stained sections showed an unstained central core with a deeply stained rim in the center of each muscle fiber (Fig. 1b). The central core was weakly stained by Gomori trichrome (Fig. 1c), cytochrome *c* oxidase (Fig. 1d) and PAS (Fig. 1E) staining.

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Acid phosphatase activity was increased in the core (Fig. 1f). In the ATPase-stained sections almost all the muscle fibers were shown to be type 1.

Electron microscopically, myofilaments outside of the central core were not disarranged and Z disks ran at right angles to the myofilament array. Inside of the cores, however, myofilaments and Z disks were disarranged (Fig. 2). Mitochondria and glycogen granules were greatly decreased. At the edge of the cores, swollen mitochondria and an increase in glycogen granules were observed.

DIAGNOSIS

Central core disease.

DISCUSSION

This 15-year-old boy was born as a floppy infant. After birth his physical development was delayed. A muscle biopsy revealed a central core in the center of each muscle fiber. From the typical clinical course and histopathological findings, it is easy to diagnose this case as central core disease.

Central core disease was first reported by Shy and Magee in 1956.[1] In 1958 Greenfield *et al.* adopted this term.[2] Denborough *et al.* described a case of central core disease combined with malignant hyperthermia.[3] In 1990 MacLennan *et al.* reported that the ryanodine receptor gene is a candidate for predisposition to central core disease and malignant hyperthermia.[4] To date more than 10 ryanodine receptor mutations associated with central core disease and malignant hyperthermia have been identified.

There are two possibilities regarding the pathogenesis of central core disease. One is the neuronal reinnervation theory, because almost all the muscle fibers are type 1 and the central cores resemble the target fibers occurring at the time of reinnervation. The other is the abnormal ryanodine receptor theory, which proposes that calcium is over-released from sarcoplasmic reticulum and damages

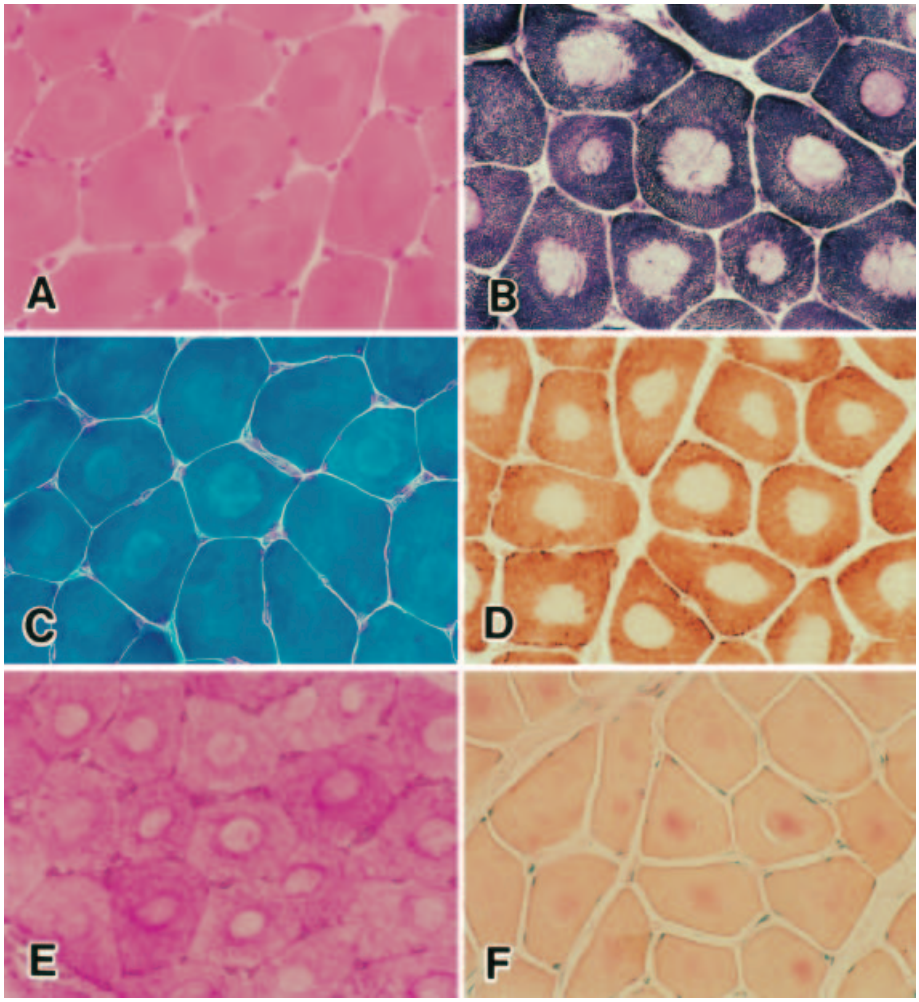

Fig. 1 (**a**) HE-stained section showing mild variation in the diameter of muscle fibers. The center of each muscle fiber is deeply stained with a pale stained halo. (**b**) NADH-TR-stained section showing an unstained central core with a deeply stained rim in the center of each muscle fiber. (**c**) The central core is weakly stained by Gomori trichrome staining. (**d**) The central core is weakly stained by cytochrome *c* oxidase staining. (**e**) The central core is weakly stained with a deeply stained rim by PAS staining. (**f**) Acid phosphatase activity is increased in the core.

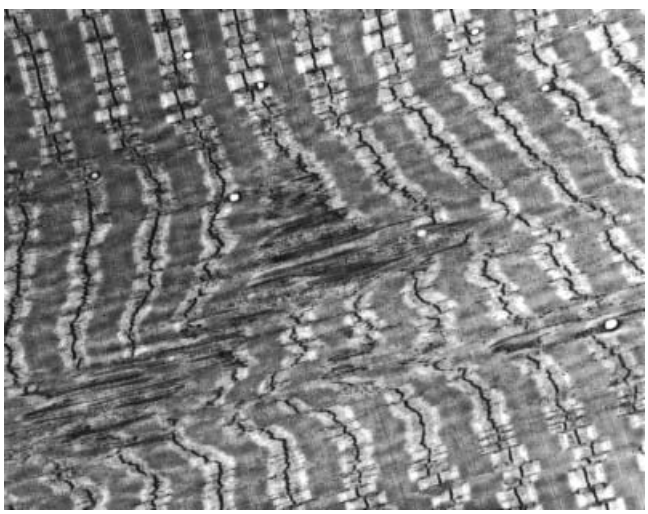

Fig. 2 Electron microscopic analysis reveals that myofilaments outside of the central core are not disarranged and Z disks run at right angles to the myofilament array, while myofilaments and Z disks are disarranged inside of the core (×5700).

mitochondria, resulting in disarrangement of myofilaments in the center of the muscle fibers.[5]

In the near future gene therapy will be adopted when the gene responsible for this disease is identified.

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