CENTRAL CORE MYOPATHY WITH AUTOPHAGY

Central core disease (CCD) is a congenital myopathy that presents with areas devoid of mitochondria on muscle biopsy, called cores.1 Congenital myopathies with cores may be associated with mutations in the ryanodine receptor 1, selenoprotein 1, alpha skeletal muscle actin, titin, myosin heavy chain 7, and Kelch repeat and BTB domain containing 13 genes.1

We describe a 28-year-old man with developmental delay since birth. He achieved independent gait at 2 years of age but had lower limb weakness. Currently, he has difficulty with standing up and raising his arms, and he has myalgia after prolonged exercise. Physical examination showed that he had normal facial strength but had proximal weakness and atrophy of the upper and lower limbs (grade 4, Medical Research Council). Electromyography showed that he had myopathic motor unit potentials in the majority of muscles. The creatine kinase and aldolase levels were normal.

Muscle biopsy demonstrated type 1 fiber predominance; numerous eccentric cores on cytochrome c oxidase, succinate dehydrogenase, and nicotinamide adenine dinucleotide, reduced, reactions; autophagic vacuoles; sparse myofiber splitting; and focal increased acid phosphatase activity in areas of the myofiber that lacked cores (Fig. 1).

By performing molecular studies with a customized next generation sequencing panel for 88 genes involved in neuromuscular disorders, we identified a heterozygous c.14677 C>T (p.R4893W) mutation in exon 101 of the RYR1 gene that was not present in his parents. His 2 children, ages 6 and 2 years, started walking at approximately the age of 1 year and are currently asymptomatic.

Authophagic vacuoles are secondary lysosomes limited by membranes that contain cytoplasmic degradation products. Autophagic vacuoles may occur in inflammatory myopathies, lysosomal storage disorders, toxic myopathies, channelopathies, myofibrillar myopathy, oculopharyngeal muscular dystrophy, and vitamin E deficiency.2 However, they are not a common feature in CCD.

The pathogenic RYR1 mutation identified in this patient had previously been described in 2 patients with an autosomal dominant inheritance pattern.3 In those patients, unique eccentric cores were observed, but there was no description of autophagy. The case described here, therefore, broadens the phenotype of RYR1 mutations.

The diagnosis of RYR1-related CCD is very relevant for genetic counseling, and this patient carries a 50% risk of having a new offspring who carries the mutation. In addition, his 2 children also have a 50% probability of having inherited the deleterious mutation. According to the guidelines for genetic testing of healthy children of the American Society of Human Genetics,4 predictive tests in asymptomatic children are not recommended. Discussion of this topic with the patient is an essential part of required genetic counseling.

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Abbreviations: CCD, central core disease; RYR1, ryanodine receptor 1 gene

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FIGURE 1. Muscle biopsy. (A) Myofiber splitting (arrow; HE × 400). (B) Internal nuclei and myofiber splitting (arrow; modified Gomori trichrome × 400). (C) increased acid phosphatase activity (arrow; acid phosphatase × 200). (D) Unique eccentric cores (arrowheads; SDH × 200). (E) Structured core (transmission electron microscopy × 3,000). (F) Autophagic vacuole (arrow; transmission electron microscopy × 10,000). HE, hematoxylin and eosin; SDH, succinate dehydrogenase.

REFERENCES


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