Central core myopathy with autophagy

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Ethical Publication Statement

All authors of this manuscript confirm that they have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.
Keywords

Congenital myopathy – central core myopathy – autophagy – RYR1 – muscle histopathology
Central core disease (CCD) is a congenital myopathy that presents with areas devoid of mitochondria on muscle biopsy, called cores\textsuperscript{1}. Congenital myopathies with cores may be associated with mutations in the RYR1, SEPN1, ACTA1, TTN, MYH7, and KBTBD13 genes\textsuperscript{1}.

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

Muscle biopsy demonstrated type 1 fiber predominance, numerous eccentric cores on COX, SDH, and NADH reactions, autophagic vacuoles, sparse myofiber splitting, and focal increased acid phosphatase activity in areas of the myofiber that lacked cores (Figure 1).

Molecular studies using a customized next generation sequencing panel for 88 genes involved in neuromuscular disorders identified a heterozygous c.14677 C>T (p.R4893W) mutation in exon 101 of the RYR1 gene, which was not present in his parents. His two children, aged 6 and 2 years, started walking around 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\textsuperscript{2}. However, they are not a common feature in CCD.

The pathogenic RYR1 mutation identified in this patient has previously been described in 2 patients with an autosomal dominant inheritance pattern\textsuperscript{3}. In those patients, unique

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eccentric cores were observed, but there was no description of autophagy. The case describe 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 probability of 50% 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 important part of necessary genetic counseling.

**Conflicts of interest**

None of the authors has any conflict of interest to disclose. All authors have read and approved the submitted manuscript.

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List of abbreviations

CCD – Central Core disease

RYR1- Ryanodine Receptor 1 gene

SEPN1 – selenoprotein 1 gene

ACTA1- alpha skeletal muscle actin gene

TTN – Titin gene

MYH7 - Myosin Heavy Chain 7

KBTBD13 - Kelch Repeat And BTB Domain Containing 13

MRC - Medical Research Council

COX - Cytochrome c oxidase

SDH - succinate dehydrogenase

NADH - Nicotinamide adenine dinucleotide, reduced

References


Figure legend

**Figure 1. Muscle biopsy.** (A) Myofiber splitting (arrow), (B) internal nuclei and myofiber splitting (arrow), (C) increased acid phosphatase activity (arrow), (D) unique eccentric cores (arrows), (E) structured core, (F) autophagic vacuole (arrow) (A: HE 400x; B: modified Gomori trichrome 400x; C: acid phophatase 200x; D: SDH 200x; E and F: transmission electron microscopy, E – 3000x, F – 10000x).

Figure 1

1361x1619mm (96 x 96 DPI)