Recurrent rhabdomyolysis and an autosomal dominant family history of scoliosis: clinical features leading to a diagnosis of metabolic myopathy

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Exertional rhabdomyolysis is typically associated with metabolic or mitochondrial myopathies; however, there are important causes such as muscular dystrophies. Herein we describe a case of recurrent exertional rhabdomyolysis in which the diagnosis of RYR1 associated disease was made on clinical presentation avoiding the need for extensive or invasive investigation.

A 29-year-old man experienced six episodes of self-limiting muscle contractures and myoglobinuria over several years. Each episode occurred 1 to 3 weeks after significant exercise or dehydration with marked alcohol consumption, though we suspect a more proximal trigger due to recall bias. The most recent episode occurred after a week of intensive road cycling in the French Alps. On returning home, his creatine kinase (CK) was found to be 30,000 U/L. Review of previous blood test revealed that his transaminases had been intermittently raised over several years. He reported no exertional symptoms during childhood or adolescence. The only family history of note was scoliosis affecting his mother and maternal aunt. Examination revealed spinal rigidity and subtle contractures of the finger flexors, hip extensors, and ankle dorsiflexors and was otherwise unremarkable including strength and lack of scoliosis.

Based on the clinical presentation of delayed onset of recurrent rhabdomyolysis and joint contractures, spinal rigidity and a family history of scoliosis, a clinical diagnosis of RYR1 associated neuromuscular disease was suspected. Muscle imaging with MRI did not show associated changes. Molecular genetic panel testing revealed a known pathogenic heterozygous sequence change in exon 39 of RYR1 (c.6488G>A;p.Arg2163His). Family testing confirmed that his mother and maternal aunt carried the same pathogenic variant in RYR1. The patient has been followed up for over 24 months since diagnosis. During this time, he has experienced further, but less frequent, episodes of rhabdomyolysis due to avoiding triggers including over exercising, alcohol, and dehydration.

It is estimated that pathogenic variants in RYR1 account for more than one third of unexplained rhabdomyolysis events [1]. Despite this, the examination findings indicative of the diagnosis are not widely known, possibly because pathogenic variants in RYR1 are associated with varied phenotypes and histopathology. Clinical phenotypes can include malignant hyperthermia syndrome (MHS), proximal muscle weakness, scoliosis, contractures, and rhabdomyolysis [2]. The histopathology on muscle biopsy is equally diverse and includes central core disease, multiminicore disease, centronuclear myopathy, core-rod myopathy, and congenital fibre-type disproportion [3]. The pathogenic variant in this case has been described in association with central core disease and MHS [2,4&5], but never with exertional rhabdomyolysis as the presenting symptom. Nine UK families were identified to carry this pathogenic variant after an index case developed MHS following general anaesthesia [3].

The key messages we wish to convey are first, the importance of careful examination for contractures in the context of recurrent rhabdomyolysis, as this can avoid the need for extensive and invasive investigation. Early contractures are associated with several inherited muscle disorders most notably collagen VI disease, Emery-Dreifuss muscular dystrophy and rarely spinal rigidity can be seen with other metabolic myopathies. Secondly, the classification of RYR1 mutations is challenging, particularly with a variant of unknown significance, and invitro contracture testing may be considered. If patients do not wish to proceed with biopsy, patients and their families should be warned about the risk of MHS.

References

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