Amyloidosis and exercise intolerance in *ANO5* muscular dystrophy

Margherita Milone[1], Teerin Liewluck[1], Thomas L. Winder[2], Paolo T. Pianosi[3]

[1]*Neurology and* [3]*Pediatrics Departments, Mayo Clinic, Rochester MN, USA*

[2]*PreventionGenetics, Marshfield, WI, USA*

Introduction: Mutations in anoctamin 5 (*ANO5*) and dysferlin (*DYSF*) genes can result in limb girdle muscular dystrophy or distal myopathy with weakness and atrophy of the calf muscles. Amyloid deposits can occur in the skeletal muscle of patients with dysferlinopathy. We investigated the molecular defect of a patient with myopathy and amyloid deposits in skeletal muscle and no evidence of systemic amyloidosis.
Methods: Clinical observations, histochemical, immunocytochemical and biochemical studies of skeletal muscle and mutation analysis.
Results: A 53-year-old woman had exercise-induced myalgia and fatigue since childhood. Later in life she developed limb weakness. In addition, she was experiencing exercise-induced exacerbation of the baseline weakness to the point that at time she was unable to climb small steps. Neurological examination revealed a mild symmetric weakness of the proximal limb muscles and foot dorsiflexor muscles, inability to walk on toes and diffuse muscle atrophy, more pronounced in the left calf muscles. CK values had been fluctuating between 444 and 22,000 U/L (nl 38-176 U/L) with the highest values being detected after intense physical activity and accompanied by elevated serum myoglobin. Muscle biopsy showed mild nonspecific myopathic changes and amyloid deposits within the blood vessel walls and around muscle fibers. Mutation analysis identified two heterozygous mutations in *ANO5*, the common c.191dupA (p.Asn64Lysfs*15) and the missense mutation c.2018A>G (p.Tyr673Cys). Her asymptomatic parents carry one of the two mutations. Dysferlin immunoreactivity was normal in muscle and sequencing of the *DYSF* gene identified no pathogenic mutation. Biochemical assay of glycolytic enzymes, carnitine palmytoil transferase 2, coenzyme Q10 and mitochondrial respiratory chain complexes in muscle was normal.
Conclusions: Anoctaminopathy 5 and dysferlinopathy can share not only the clinical phenotype, but also the pathological feature of amyloid deposits in muscle, raising the possibility of interaction between the sarcolemmal dysferlin and the intracellular membrane-associated anoctamin 5.