Skeletal muscle involvement in patients with truncations of titin and familial dilated cardiomyopathy

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Background: Variants in TTN are associated with dilated cardiomyopathy (DCM) and skeletal myopathy with or without cardiac affection. However, the skeletal muscle phenotype has not been systematically evaluated in patients with predisposition to or manifest cardiac involvement due to heterozygous truncating TTN variants (TTNtv), the most common cause of DCM.

Purpose: Assess the skeletal muscle phenotype associated with TTNtv.

Methods: This cross-sectional study examined skeletal muscle involvement in individuals with TTNtv by quantifying and comparing fat fraction from muscle magnetic resonance imaging to controls (matched on body-size, sex, and age), and evaluating muscle strength by dynamometry and features from muscle biopsies.

Results: Twenty-five participants (11 women, age 51 ± 15 years, left ventricular ejection fraction 45 ± 10%) with TTNtv were included (19 had DCM). Compared to controls, participants with TTNtv had higher fat fraction in calf- (12.5% vs 9.9%, p = 0.013), thigh- (12.2% vs 9.3%, p = 0.004) and paraspinal muscles (18.8% vs 13.9%, p = 0.008), see figure. Muscle strength was relatively intact (within 1 SD of normal values). Muscle biopsies in 21 participants showed that 13 (62%) displayed myopathic features, most notably an increased proportion of central nuclei. Electron microscopy showed well-ordered Z-lines and T-tubuli but uneven and discontinuous M-lines and excessive glycogen depositions flanked by large autophagosomes, lysosomes, and abnormal mitochondria with mitophagy.

Conclusion: Skeletal muscle involvement is prevalent in patients with cardiac involvement or predisposition to DCM due to TTNtv and is characterized by an increased muscle fat fraction, and excessive accumulation of glycogen, possibly due to reduced autophagic flux. This emphasizes the need for specialized diagnostic work-up in patients with TTNtv, especially if reporting symptoms or objective signs of muscle involvement.