"Necklace" fibers, a new histological marker of late-onset MTM1- related centronuclear myopathy

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Mutations in the gene encoding the phosphoinositide phosphatase myotubularin 1 protein (MTM1) are usually associated with severe neonatal X-linked myotubular myopathy (XLMTM). However, mutations in MTM1 have also been recognized as the underlying cause of "atypical" forms of XLMTM in newborn boys, female infants, female manifesting carriers and adult men. We reviewed systematically the biopsies of a cohort of patients with an unclassified form of centronuclear myopathy (CNM) and identified four patients presenting a peculiar histological alteration in some muscle fibers that resembled a necklace ("necklace fibers"). We analyzed further the clinical and morphological features and performed a screening of the genes involved in CNM. Muscle biopsies in all four patients demonstrated 4 - 20% of fibers with internalized nuclei aligned in a basophilic ring (necklace) at 3 ?m beneath the sarcolemma. Ultrastructurally, such necklaces consisted of

myofibrils of smaller diameter, in oblique orien