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Floppy infant syndrome as a first manifestation of LMNA-related congenital muscular dystrophy

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Abstract

LMNA-related congenital muscular dystrophy (L-CMD) is the most severe phenotypic form of skeletal muscle laminopathies. This paper reports clinical presentation of the disease in 15 Polish patients from 13 families with genetically confirmed skeletal muscle laminopathy. In all these patients floppy infant syndrome was the first manifestation of the disease. The genetic diagnosis was established by next generation sequencing (targeted panel or exome; 11 patients) or classic Sanger sequencing (4 patients). In addition to known pathogenic LMNA variants: c.116A > G (p.Asn39Ser), c.745C > T (p.Arg249Trp), c.746G > A (p.Arg249Gln), c.1072G > A (p.Glu358Lys), c.1147G > A (p.Glu383Lys), c.1163G > C (p.Arg388Pro), c.1357C > T (p.Arg453Trp), c.1583C > G (p.Thr528Arg), we have identified three novel ones: c.121C > G (p.Arg41Gly), c.1127A > G (p.Tyr376Cys) and c.1160T > C (p.Leu387Pro). Eleven patients had de novo mutations, 4 - familial. In one family we observed intrafamilial variability of clinical course: severe L-CMD in the male proband, intermediate form in his sister and asymptomatic in their mother. One asymptomatic father had somatic mosaicism. L-CMD should be suspected in children with hypotonia in infancy and delayed motor development, who have poor head control, severe hyperlordosis and unstable and awkward gait. Serum creatine kinase may be high (~1000IU/l). Progression of muscle weakness is fast, leading to early immobilization. In some patients with L-CMD joint contractures can develop with time. MRI shows that the most frequently affected muscles are the serratus anterior, lumbar paraspinal, gluteus, vastus, adductor magnus, hamstrings, medial head of gastrocnemius and soleus. Ultra-rare laminopathies can be a relatively common cause of generalized hypotonia in children. Introduction of wide genome sequencing methods was a breakthrough in diagnostics of diseases with great clinical and genetic variability and allowed approach "from genotype do phenotype". However target sequencing of LMNA gene could be considered in selected patients with clinical picture suggestive for laminopathy.

Keywords: Dropped head syndrome; Floppy infant; L-CMD; LMNA gene; LMNA-Related congenital muscular dystrophy; Laminopathy.

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