Neonatal cardiomyopathy caused by double mutation in RAS pathway genes.

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Introduction: Severe myocardial hypertrophy in children, and especially, in infants, needs more extensive diagnostic work up due to the wide spectrum of inborn errors of metabolism, monogenic syndromes and microchromosomal aberrations. Pediatric patients with hypertrophic cardiomyopathy diagnosed in the first six months of life represent a group with the poorest prognosis and very limited treatment options. Every such case needs the personalized approach in terms of arrhythmia management, surgical interventions and genetic canceling.

Results: A 5-month boy was hospitalized due to obstructive hypertrophic cardiomyopathy diagnosed right after birth. He was born in term with Cesarean cessation due to the mother’s age. Myocardial hypertrophy was reveal on week 28 of gestation during schedules ultrasound. The patient had no signs of dismorphism, lactate level and other biochemical parameters were normal. The inborn metabolic disorders were excluded by mass spectrometry metabolite tests and standard cytogenetic analysis confirmed 46XY karyotype. Serial echocardiography performed during the first year demonstrated severe increase in myocardial thickness with critical left ventricular outflow tract obstruction that gradually deteriorated with time. Morphological examination of the myocardial sample obtained during Ross-Cohn operation revealed gross myocardia fibrosis and myofibrillar disarray. To identify a genetic cause of severe inborn hypertrophic cardiomyopathy we performed a target sequencing of 108 genes associated with cardiomyopathies, arrhythmic disorders and several metabolic disorders using NGS approach on MiSeq instrument after Haloplex target enrichment. Two mutations in the genes of RAS-signaling pathway were detected. The first one, Y279C in PTPN11 was previously reported in a patient with LEOPARD syndrome. The second one is a new R585L substitution in CBL gene, which is associated Noonan-like syndrome. Both genes participate in the intracellular RAS signaling pathway that contributes to the cell proliferation and hypertrophy in response to extracellular grow factor stimulation. Mutations in the RAS-pathways genes lead to the group of clinically overlapping disorder called “RASopathies” which often involve myocardial hypertrophy, congenital heart disorders, ectodermal abnormalities and tumors. To our knowledge this is the first report of combined double mutations in the genes of RAS-pathway in a patient with hypertrophic cardiomyopathy. Conclusions: We conclude, that severe neonatal myocardial hypertrophy with left ventricular tract obstruction may be caused by double mutations in the genes of RAS-pathway in spite of absence of facial dimorphism and other organ abnormalities.