MUSCULAR DYSTROPHY WITH A MUTATION IN THE CAVEOLIN-3 (CAV-3) GENE

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OBJECTIVE: Raised serum creatine kinase (hyperCKaemia) is a hallmark of hereditary neuromuscular disorders (3). However, several acquired conditions (for example, infections, alcoholism, drugs, intramuscular injections) may also cause a rise in creatine kinase, and as the enzyme is now often included in routine blood tests the number of apparently healthy individuals with persistent hyperCKaemia has increased (2). Here, we present a case with persistent hyperCKaemia and CAV3 mutation .

METHOD: An 11-year-old male patient borned in nonconsangious family admitted to our hospital with the complaint of muscle cramps with exertion and fatigue. Motor milestones and general physical examination of the patient were normal. Muscle weakness (upper extremity 3/5, lower extremity 3/5), toe walking with bilateral achilles tendon retraction and mild calf hypertrophy were present in neurologic examination. On several different occasions during the last 2 years they were found to have variably, but persistently, elevated serum creatin kinase (CK, 2000-2500 U/L) and transaminase (ALT: 98 U/L, AST: 200 U/L) levels. Serum CK level was also elevated in his sister (400-800 U/L), but normal in the parents. Metabolic screening tests , cranial/spinal magnetic resonance imagings, and nerve conduction velocities were normal . Electromyography was consistent with myopathy. Both electrocardiography and heart echocardiography were normal.

RESULT: Heterozygous CAV3 c.290_292delTCT(p.Phe97del) mutation variant was revealed in clinical exome sequence analysis (WES). The patient is still receiving rehabilitation support and family genetic counseling was given.

CONCLUSION: Caveolae are flask-shaped plasma membrane invaginations (1). They are most conspicuous in adipocytes, endothelial cells, muscle cells, and fibroblasts. Although their functions are not known exactly, they are thought to be transcytosis, podocytosis and signal transduction (1). The mammalian caveolin gene family consists of caveolin-1 (CAV1), caveolin-2 (CAV2), and caveolin-3 (CAV3) (2) . CAV3 is muscle specific and expressed in skeletal, cardiac, and smooth muscle cells. Mutations in Caveolin-3 gene are known to cause muscular dystrophies that are collectively called caveolinopathies (3). Different mutations in the CAV-3 gene have been associated with various clinical phenotypes (3,4). Familial hypertrophic cardiomyopathy, Elevated serum creatine phosphokinase,, Long QT syndrome, Distal myopathy, (Tateyama type), and Limb-girdle muscular dystrophy (LGMD1C) reclassified as Rippling muscle disease (RMD 2) (Table 1). Many patients show an overlap of these skeletal muscle entities, and there are no genotype/phenotype correlations, the same mutation can cause heterogeneous phenotypes, and there is intrafamilial variability (4) . Caveolin 3 mutation should be considered in the differential diagnosis in patients with fatigue, muscle weakness, exercise-induced cramps, and hyperCKaemia (4).

Table 1: Various clinical phenotypes associated with CAV-3 gene mutation

CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC, 1; CMH1 #192600	CREATINE PHOSPHOKINASE, ELEVATED SERUM #123320	LONG QT SYNDROME 9; LQT9 #611818	MYOPATHY, DISTAL, TATEYAMA TYPE; MPDT #614321	RIPPLING MUSCLE DISEASE 2; RMD2 #606072
Asymmetric septal hypertrophy Apical hypertrophy (in some patients) Subaortic stenosis Hypertrophic cardiomyopathy Presystolic gallop Palpitation Arrhythmia Congestive heart failure Sudden death	Muscle cramps with exertion Elevated serum CPK Normal muscle biopsy Normal exercise lactic acid production	Prolongation of corrected QT interval Nonexertional syncope (in some patients) Sinus bradycardia (in some patients) Cardiac arrest (in some patients)	Muscle weakness, distal, particularly affecting the hands Muscle atrophy, distal, particularly affecting the hands Muscle biopsy shows variation in fiber size Calf hypertrophy Internal nuclei Absence of caveolin-3 staining Increased serum creatine kinase	Muscle cramps with exercise Muscle pain with exercise Muscle stiffness with exercise Muscle hyperirritability Muscle hypertrophy Muscle activity is electrically silent on EMG Percussion-induced rapid rolling muscle contractions (PIRC) Decreased CAV 3 expression on muscle biopsy

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