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CAV-3-related age-dependent muscle diseases: A novel mutation in mother and son

Hande Tekin *MD*, Pınar Edem *MD*

Department of Pediatric Neurology, Bakircay University Faculty of Medicine, Izmir, Turkey

Abstract

The caveolin-3 protein encoded by the CAV-3 gene is a muscle-specific protein found in skeletal, smooth, and cardiac muscle. Caveolin-3 defects lead to several muscle diseases: rippling muscle disease (RMD), limb-girdle muscular dystrophy (LGMD1C), distal myopathy, familial hypertrophic cardiomyopathy, and asymptomatic hyper-CK-emia. While some variants that cause mutations in this gene cause a pure type of disease, some variants may appear as overlap syndromes. Even in the same variants of CAV-3 mutation, the type of muscle disease, its severity, and time of occurrence can be variable. For this reason, it should be known that CAV-3-related diseases and all overlapping diseases can be seen over time, and the patient should be followed up. We report here a 9-year-old boy and his 38-year-old mother who were investigated for asymptomatic hyper-CK-emia and diagnosed with caveolinopathy. The boy had calf hypertrophy and percussion-induced rapid muscle contraction (PIRCs). His mother had calf hypertrophy, contractions due to percussion, and proximal muscle weakness. Mother's proximal muscles and m. gastrocnemius magnetic resonance imaging (MRI) was normal. The mother had complaints of weakness, showing slow progression starting from the second decade. Heterozygous (ENST000003cav3849.2) c.298A>T p.Ile100Phe variant in exon 2 was detected in the CAV-3 gene. This mutation is classified as pathogenic according to The American College of Medical Genetics and Genomics (ACMG) criteria (PM1, PM2, PP3, PM5). In conclusion, calves' pseudohypertrophy and mildly raised CK without weakness can be the initial presentation of caveolinopathy. Percussion-induced muscle contractions, rather than muscle rippling, can occur at a young age. The onset of muscle weakness can be delayed during adolescence and can have a slowly deteriorating course associated with myalgia.

Keywords: CAV-3, children, percussion-induced rapid muscle contraction (PIRCs), LGMD1C

INTRODUCTION

Caveolin-3 gene mutations cause clinically distinct autosomal dominant muscle diseases. Limb-girdle muscle disease 1C (LGMD-1C), rippling muscle disease (RMD), familial or sporadic asymptomatic hyper creatinine kinase (hyper-CK-emia), distal myopathy (DM), familial hypertrophic cardiomyopathy (HCM), and arrhythmogenic long QT syndrome are caveolinopathies that occur with different frequencies.[1-3]

The Cav-3 protein contains four distinct domains. These are N-terminal (aa 1-53), scaffolding (aa54-73), transmembrane (aa74-106), and C-terminal (aa107-151). However, the location of the mutation could not be associated with the phenotypes in muscle diseases. While these diseases may present individually with their specific clinical features, they may also appear to overlap diseases associated with CAV-3 mutation.[3] All these autosomal dominant muscle diseases can occur in the same patient over time. Therefore, the prominent symptoms of patients of different ages may be different. The common feature of all these Cav-3-related diseases is hyper-CK-emia. Asymptomatic CK elevations, calf hypertrophy, leg pain, and cramps can be observed at early ages. Proximal muscle weakness and spontaneous or stimulus RMD may be added to these findings in advancing ages. Rippling muscle disease is characterized by signs of increased muscle irritability, such as percussion-induced rapid contraction (PIRC), percussion-induced muscle mounding (PIMM), and mechanically induced muscle rippling contractions.[1] All three stimulus-related muscle contraction responses in RMD, the presence of only one is sufficient for diagnosis. It

Address correspondence to: Hande Tekin, MD, Assoc Prof, Bakircay University Faculty of Medicine, Department of Pediatric Neurology, Izmir, TURKEY. Tel: +905055985681, email: gazetecihande@yahoo.com.tr

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occurs only with CAV-3 gene mutation. Clinical detection of RMD can be challenging as the percussion response is often not checked routinely during examination, and the muscle contraction can be easily confused with the clinical myotonia too.

Calf hypertrophy is a feature detected at an early age and observed in almost all caveolinopathies. Caveolin-3 participates in preservation of sarcolemmal integrity, signaling pathways and regulation of myocyte growth, repair and muscle hypertrophy through its interactions with other proteins such as dystrophin, sarcoglycans, dystroglycans, dysferlin, phosphofructokinase, and neuronal nitric oxide synthase.[1,4] In Cav-3 deficiency, impairments in these functions result in cellular injury and muscular atrophy. For example, in Cav-3 mutant mice (P104L) significantly increased neuronal nitric oxide synthase and over-activation of myostatin-signaling pathway are shown; both of which are known to cause cell damage.[3,5] Therefore accompanying calf hypertrophy in caveolinopathies might be developing secondary to impaired hypertrophy-atrophy balance and accompanying cell damage. Defective associations between these proteins can cause many muscle diseases. Many disease phenotypes are encountered in CAV-3 mutations, as changes in the structure of caveolae will also vary in the structure of these proteins at different rates.

We present in this report caveolinopathies detected in the son and his mother with incidental hyper-CK-emia.

CASE REPORTS

Patient 1

A 9-year-old male patient, the only child of an unrelated family, was referred because of the detection of hyper-CK-emiaemia (764IU/l) in his routine examinations.

He did not have any muscle cramps, weakness, or fatigue. He had no complaints when climbing stairs, standing up from a sitting position, or post-exercise. Motor milestones were normal.

There is no history of recent infection or injection. There was moderate calf hypertrophy and muscle contraction with percussion, there was no atrophy in any muscle group (video 1) in the examination. Sensory examination was normal. There was no Gower's sign, muscle strength and tone were normal. Deep tendon reflexes were normal. The patient's cognition, motor performance, and behavior were normal.

Multiplex Ligation-dependent Probe Amplification (MLPA) was normal in the DMD gene. Echocardiography, Electrocardiogram, and Holter monitoring were normal. The patient had rapid contractions in both upper and lower extremity muscles with percussion. There was no rippling or mounding after percussion and rapid contraction. In the examination of the patient's parents, while the father's examination and CK were normal, the mother had findings suggestive of muscle disease and hyper-CK-emia.

Patient 2

A 38-year-old female patient, mother of Patient 1, had no consanguinity between her parents. While her son was being examined for hyper-CK-emia, her blood creatinine kinase level was elevated in two separate examination (1245 – 1007 IU/l). In the upper extremity examination, it was observed that the muscle strength of the M. Deltoideus and shoulder junction muscles was 4/5. Forearms and trunk muscle strength were normal. In the lower extremity examination, hip flexion, extension, thigh abduction, and adduction were of 4/5 muscle strength. Muscle weakness was evident, especially in the proximal muscles of the lower extremities. Deep tendon reflexes were normal. She could stand on the tips of his toes and heels. Gower's sign was negative. There was bilateral calf hypertrophy (Figure 1).

Due to her weakness in her upper extremity, she could not carry 1-2 kg objects. Percussion-induced rapid muscle contraction (PIRCs) was present in the patient's muscles (video 1). There was no atrophy in the thenar-hypothenar and foot muscles. Sensory examination was normal.

Her complaints started at the beginning of the first decade as she experienced weakness in the arms, falling behind her classmates while running, and getting tired quickly. She had been receiving various nutritional support for the last 10 years due to muscle cramps, but her cramps did not improve. Although she did not experience any problems in her daily activities, she could not run, had muscle cramps, and felt tired towards the end of the day.

The muscle group with the most complaints was the lower extremity group which was imaged with MRI. There were no findings in favor of atrophy, fat degeneration, and increased connective tissue in both thigh and leg muscles. The cognitive and psychiatric evaluation of the patient, an industrial engineer speaking three different languages, was normal.

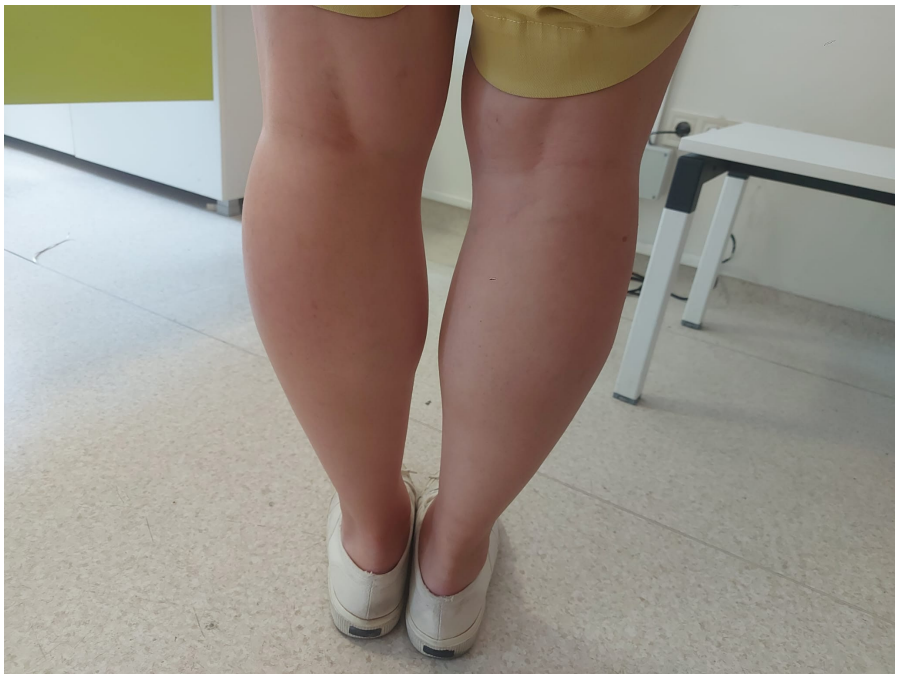

Figure 1 : Bilateral calf hypertrophy

Echocardiography, Electrocardiogram, and Holter monitoring were normal.

Nerve conduction velocity was normal. Needle EMG showed myopathic motor unit potentials of decreased duration and amplitude on volition in the upper and lower extremity proximal muscles. Myotonia and spontaneous activities were not observed in any of the muscles. PIRCs were associated with bursts of normal motor unit action potentials.

From the neuromuscular panel new generation sequencing analysis, which included 85 genes sent from the patient and her son, the novel mutation in which the heterozygous c.298A>T p.Ile100Phe variant in exon 2 was detected in the CAV-3 gene. It was recorded and interpreted as "pathogenic" in ACMG criteria (PM1, PM2, PP3, PM5).

The CK values of the patient's brother and his children were found to be normal.

Physical therapy and rehabilitation processes were initiated for both patients.

DISCUSSION

Novel mutation heterozygous A>T transversion at position 298 in the second exon of CAV-3, predicting a Ile100Phe amino acid exchange, was detected in the mother and son investigated for incidentally detected hyper-CK-emia. This mutation was previously unidentified and located in the gene's membrane-spanning domain. Mutations in the membrane-spanning domain of this gene can cause all CAV-3-related muscle diseases. Diseases associated with LGMD, RMD, Hyper-CK-emia, and LGMD-RMD have been described in this domain.[3]

Muscle diseases associated with mutations in the CAV-3 gene can be seen alone, such as RMD in the boy, or maybe in the form of LGMD-1C and RMD coexistence, as in the second patient. We think that proximal muscle weakness in the mother, unlike her son, is associated with advanced age. Proximal muscle weakness and muscular dystrophy-like clinical findings previously described for the CAV-3 gene were named LGMD 1C. However, when looking at large patient series over time, it has been observed that RMD-related diseases have hyper-CK-emia, calf hypertrophy, rapid muscle contractions with percussion at an early age, but in the following years, signs of weakness in the junctional muscles or distal myopathy occur in these patients.[1,2,6-8]

Not surprisingly, the mutation in the CAV-3 gene involves clinical manifestations similar to muscular dystrophy. The CAV-3 mutation we detected interacts with the DAG-1 gene in the 64-114 amino acid region. DAG-1 gene encodes dystroglycan, a central component of the dystrophin-glycoprotein complex that links the extracellular matrix and the cytoskeleton in the skeletal muscle. Mutations in this gene cause

distinct forms of muscular dystrophy.[9]

In Duchenne muscular dystrophy (DMD), the upregulation of cav-3 has been proposed to be a part of the compensatory process which unfortunately increases the degradation of the dystrophin-glycoprotein complex.[4] Likewise, in animal models hyperexpression of CAV-3 resulting in increased formation of the the wild-type caveolin-3 has been shown to reduce the production of dystrophin and related glycoproteins.[10,11] Interestingly, in transgenic mice with P104L mutation, although the amount of Cav-3 decreases in muscle, hyperexpression of the mutant m-RNA with the wild-type Cav-3 m-RNA were demonstrated.[5] Mutant forms enhance the accumulation and degredation of the wild-type Cav-3 in the Golgi apparatus, preventing it to target to the plasma membrane. Thus, as mentioned earlier, myocyte damage may be caused by alterations in different aspects, including energy metabolism, cell growth and repair, in which Cav-3 plays a role.[3-5] The molecular mechanisms of the CAV-3 mutations causing dystrophic findings still need further elucidation.

While there were no RMD findings in the P104L variant located at the locus close to the mutation in our patients, LGMD 1C findings, calf hypertrophy and hyper-CK-emia were defined.[6] In the A92T variant, which is at a locus close to the variant in our patients, a similar clinic to the 2nd patient was observed.[7] As seen in these examples, there is not always a relationship between locus location and phenotypic similarity.

R26Q variant was reported in children with elevated creatine kinase without being characterized by neuromuscular symptoms.[12] Patient 1 was 9 years old and presented with hyper-CK-emia without any complaints, just like children with this variant. However, moderate calf hypertrophy and percussion-induced rapid muscle contraction were noticed upon careful examination. PIRC, which even the patient is unaware of, is a very important clue for the diagnosis that may be overlooked if the clinician is not aware of it. In the early stages of the disease, no other clinical finding other than PIRC may be encountered. This examination should be performed in children with asymptomatic CK elevation by hitting different muscle groups with a hammer.

The P104L, G55S, C71W, and R125H variants have been previously associated in the literature with isolated LGMD1C.[6,7] The common features of all patients in this group are early-onset calf hypertrophy, muscle cramps, and proximal muscle weakness in advanced ages. Patient 2 had muscle cramps and pain starting from the 2nd decade, proximal muscle weakness since the 3rd decade, and calf hypertrophy and PIRC findings of which she was not aware. Caveolinopathies are a group of diseases that show a different clinical manifestation from asymptomatic hyper-CK-emia to severe muscle diseases. CAV-3 gene mutation can manifest clinically differently, even in family members carrying the same variant. In some variants, while a limited number of clinical features are observed at a young age, different clinical findings may be detected as the age progresses. Another muscle disease that should be excluded from the differential diagnosis is distal myopathy. Palmar grip strength was normal in our patients, and there was no weakness in the opponens pollicis and dorsal interossei muscles. There was no atrophy or sensory defect in the foot muscles. In cases of CAV 3-related distal myopathy, patients have hyper CK and muscle hyperexcitability in childhood but subsequently develop distal atrophy, but they do not have calf hypertrophy as in our patient.[2]

Instead of calling it LGMD1C, RMD, or DM, we believe that it would be more correct to call these muscle diseases, which even the same variants have different clinical manifestations that change over time, i.e., CAV-3-related muscle diseases.

While RMD is detected in CAV 3-related muscle diseases at young ages, distal myopathy and LGMD1C occur at older ages in individuals with the same mutation. This is thought to be related to the dystrophic process of distal myopathy and LGMD that develops over time, whereas conditions such as percussion-induced contractions and mounding are due to a physiological effect originating from ion interactions within the cell. We know that patients with CAV-3 mutation have a phenotype that can progress from asymptomatic hyper-CK-emia. Therefore, the patient's completely normal examination findings in the first examinations which may be asymptomatic hyper-CK-emia, may progress to LGMD and DM at later age. For this reason, intermittent follow ups should continued, even if there are no symptoms. In addition, CK and muscular hyperexcitability should be investigated in the family members of these patients. While the severe course and cardiomyopathy are expected in patients with homozygous mutations in CAV 3-related RMD, those with heterozygous mutations, as in our patients, have a more benign course.[7]

Extra-extremity muscle involvement may also occur, such as ophthalmoparesis reported with RMD with a CAV 3 mutation and dilated cardiomyopathy reported with LGMD1C. Sudden infant death syndrome and Long QT syndrome should be looked for in these patients.[3] We did not find any extra-extremity muscle involvement in our patients.

In these patients, gene panels and whole exome sequencing are helpful in diagnosis, but it would be appropriate to find clues for single gene analysis due to the high cost. Hyper-CK-emia, muscle pain and weakness are nonspecific findings that can be seen in many patients. However, if every hyper-CK-emia patient is examined for RMD findings, diagnosing these patients will be much easier.

The common feature of all caveolinopathy is hyper-CK-emia. Calf hypertrophy is found in most patients, whether the patient has the RMD or LGMD phenotype at an early age. Toward the end of the first decade, most patients begin to experience muscle cramps and pain. If the caveolinopathy variant is to cause RMD, muscle hyperexcitability can often be detected at the end of the first decade. Proximal muscle involvement usually begins at the end of the second decade. Distal myopathy begins to be detected in the 5th decade. While only one of these conditions can be observed in patients, all of them can be followed over time in a patient. Some authors define this condition as a 'clinical continuum' and emphasize that all these muscle diseases may occur over time.[7] Therefore, since our patients are still young, they may develop distal myopathy at later age.

In conclusion, caveolinopathies may manifest with different clinical presentations at different age groups. Therefore, patients with hyper-CK-emia should be followed up closely to detect the changing clinical manifestations of caveolinopathies.

DISCLOSURE

Conflict of interest: None

Ethics: Informed consent was obtained from both cases and the parents of Patient 1 and Patient 2 for the publication of this report.

Video 1: Muscle contractions with percussion in Patient 1 and Patient 2. http://neurology-asia.org/content/28/3/neuroasia-2023-28(3)-751-v1.mp4

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