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CASE REPORT
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Caveolinopathy pesenting with excercise induced stiffness and transient muscle mounding

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Rippling muscle disease (RMD) is caused by dominant mutations of the caveolin-3 gene (*CAV3*), and presents with overlapping limb-girdle muscle weakness, elevated creatine kinase (hyperCKemia), RMD, and distal myopathy. We report a patient with a *CAV3* mutation who presented with myalgia, exercise-induced muscle stiffness, hyperCKemia, and percussion-induced rapid muscle contraction and muscle mounding. A familial genetic study revealed the same mutation in two family members, with physical examinations showing that both of them had rippling muscles.

Key words: Caveolin 3; Creatine kinase; Myalgia

Caveolinopathy caused by mutations of the caveolin-3 gene (*CAV3*) is associated with various overlapping muscle disorders including limb-girdle muscle weakness, elevated creatine kinase (hyperCKemia), rippling-muscle disease (RMD), and distal myopathy. RMD is characterized by percussion-induced rapid muscle contraction (PIRC), percussion-induced muscle mounding (PIMM), and mechanically induced muscle rippling. Rippling results from a wave of muscle contraction provoked by mechanical stretching of a muscle, and is electrically silent in needle electromyography.[1] Here we present a patient with caveolinopathy who presented with myalgia, exercise-induced muscle stiffness, and hyperCKemia without muscle rippling.

CASE

A 20-year-old male visited our clinic complaining of myalgia, exercise-induced muscle stiffness, and fatigability with a 10-year history. He had been healthy until the age of 10 years, when he first experienced myalgia and stiffness in his proximal leg upon running, which

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made it difficult for him to exercise. Although the stiffness resolved rapidly within 10 seconds, he subsequently was unable to perform any intense exercise. He also complained of stiffness and myalgia when waking up, which meant that he could only walk on tiptoes for the first few minutes after getting out of bed. Light repetitive exercise such as walking and grasping alleviated the symptoms. He also noticed that briskly hitting a resting limb muscle produced a transient muscle contraction and focal swelling. He also complained of daytime fatigability that was worsen by continuous exercise. He reported no other problems, including fixed or transient muscle weakness.

A physical examination revealed bilateral calf hypertrophy and that tapping limb muscle using a reflex hammer provoked a transient rapid contraction (PIRC) and focal mounding of the muscle (PIMM) (Fig. 1), but myotonia and muscle rippling were not provoked. However, a neurological examination was unremarkable, including for the individual muscle powers, deep tendon reflexes, and sensory functions.

Laboratory tests revealed a high creatinine kinase level (1,543 U/L). The findings of a nerve conduction study was normal, and needle electromyography showed some small and short motor unit potentials without abnormal spontaneous activities in all tested muscles, suggesting the presence of inactive myopathy. It was particularly interesting that when we hit the surface of a needle-inserted muscle with a reflex hammer, transient positive sharp waves and fibrillation potentials were recorded. However, no myotonic or neuromyotonic discharges were observed, and a short exercise test did not reveal any abnormality. Biopsy of the biceps muscle revealed slight variations in fiber size, a few regenerating fibers, and a slight increase in the number of internalized myonuclei (Fig. 2). Dystrophin and dysferlin immunohistochemical staining was normal.

Focused exome sequencing identified a known pathogenic variant in *CAV3* (c.80G>A [p.R27C, rs116840778]), which was confirmed by subsequent Sanger sequencing. Because the patient recalled that his older brother had enlarged calves, we performed a genetic study of his family members (father, mother, older brother, and younger sister) and identified the same mutation in his mother and elder brother. Physical examinations of his mother and older brother revealed muscle rippling, PIRC, and PIMM in both of them. Their clinical features are summarized in Table 1.

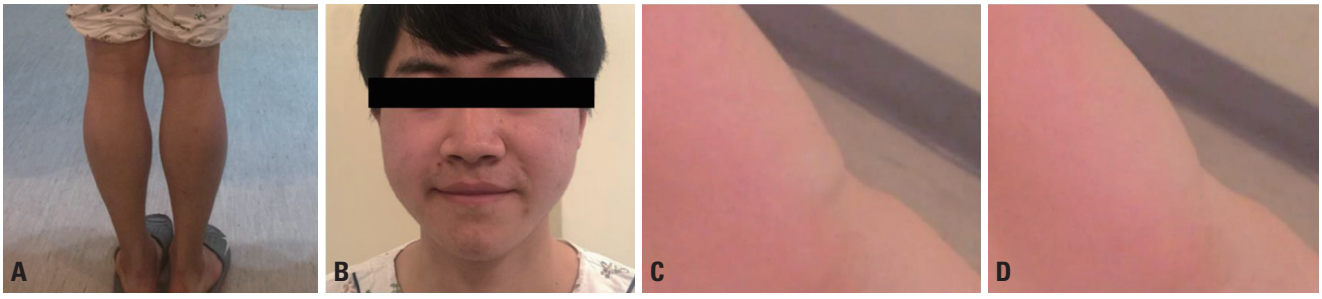

Fig. 1. Physical findings of the patient. The patient had bilateral calf hypertrophy (A), but no facial dysmorphism such as a myopathic face or high-arched palate (B). Percussion of the hypothenar muscle with a reflex hammer produced focal muscle mounding (C) that disappeared within a few seconds (D).

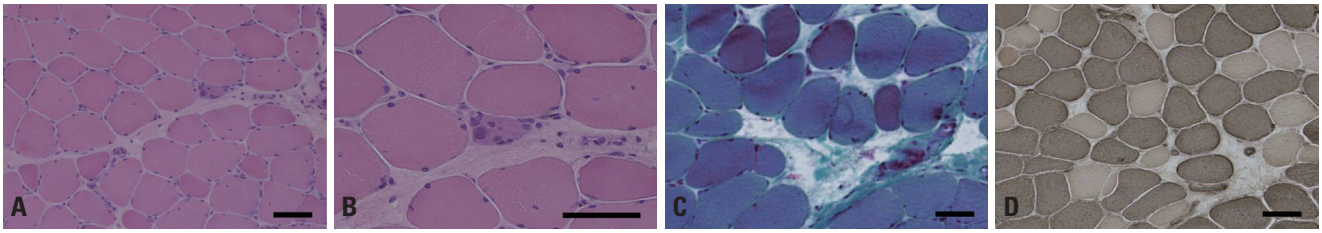

Fig. 2. Muscle biopsy taken from biceps muscle showed slightly increased numbers of internal nuclei, a few regenerating fibers, and mild muscle fiber size variation. (A) Hematoxylin and eosin statin (×200). (B) Hematoxylin and eosin statin (×400). (C) Modified Gomori-Trichrome stain (×200). (D) Adenosine triphosphatase stain at ph 10.6 (×200). The black bars represent 50 μm.

Table 1. Clinical features of the affected family members

Clinical feature	Proband	Mother	Elder brother
Onset	Teenager	Teenager	Teenager
Muscle weakness	-	-	-
Exercise induced muscle stiffness	+	+	+
Myalgia	+	-	-
Daytime fatigability	+	+	-
Calf hypertrophy	+	+	+
Percussion on muscle			
Rippling	-	+	+
Contraction and mounding	+	+	+
Serum creatine kinase level	1,543 IU/L	1,205 IU/L	1,068 U/L
Cardiomegaly or ECG abnormalities	-	-	-

IU, international unit; ECG, electrocardiogram.

DISCUSSION

In 1994, Burns et al.[2] reported a family exhibiting muscle mounding and rippling in an autosomal dominant manner and noted its benign clinical course. They also performed an electrophysiological study *in vivo* and observed an abnormal after-contraction and sarcolemmal hyperexcitability, which they suggested was responsible for the rippling muscles. In 1998, mutations in *CAV3* were first identified as a cause of limb-girdle muscular dystrophy type 1C (LGMD 1C).[3] More than 64 different mutations have been identified, and they are associated mainly with skeletal muscle disorders.[4] It is now generally accepted that there are four main distinctive phenotypes of skeletal muscle disease: limb-girdle muscle weakness, RMD, hyperCKemia, and distal myopathy.[1] It was recently proposed that LGMD 1C be excluded from the LGMD classification because its main clinical features are muscle rippling and myalgia, with RMD being proposed as a new nomenclature.[5]

Caveolin 3 is expressed in all cell types of muscle and its monomers oligomerize to form a high-molecular-mass scaffolding network that transforms sarcolemmal membranes into an invaginated structure called caveolae, which play an important role in membrane stabilization as a part of the dystrophin-glycoprotein complex, modulation of signaling pathways, and calcium and/or chloride transportation related to muscle contractions.[6] Studies of a transgenic animal model have shown that *CAV3* mutations produce pathological changes in muscles due to increased vulnerability to oxidative stress,[7] hypersensitivity to stretch forces,[6] and myofibril disorganization.[8]

The mutation identified in the present family (p.R27Q) is one of the common *CAV3* mutations. Although p.R27Q is generally associated with a milder phenotype, some patients develop fixed muscle weakness, and families with significant phenotypic variability between members have also been reported.[1] The examinations of the present family members revealed a mild phenotype with all showing features of RMD with hyperCKemia, but it is noticeable that some features such as the presence of rippling, daytime fatigability, and myalgia were not shared by all of them. In a recent large cohort of patients with caveolinopathy, myalgia was the main symptom and rippling was present in only 60% of the patients regardless of the genotype. Moreover, 40% of those patients showed muscle weakness during a 3-decade follow-up, and none of them had any respiratory or cardiac problems, suggesting that it is a very mild muscle disease.[9]

Another interesting aspect of the present patient was a needle electromyographic findings. Although it is generally believed that electrical silence is observed in rippling muscle, there are a few reports of transient spontaneous activities being present during PIRC. Maki et al.[10] observed transient bursts of asynchronous activity during PIRC, with individual potentials being very short (less than 2 milliseconds) and

resembling fibrillation potentials. Those authors considered their finding suggestive of transient hyperexcitability of individual muscle fibers during PIRC. Our findings strongly support their ideas, and so further studies are warranted to elucidate this issue.

In summary, the present case shows that the clinical presentation of caveolinopathy can be highly variable with different overlapping conditions. This should be considered in the differential diagnosis of patients with mild muscle symptoms such as myalgia and idiopathic hyperCKemia.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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REFERENCES

1. Woodman SE, Sotgia F, Galbiati F, Minetti C, Lisanti MP. Caveolinopathies: mutations in caveolin-3 cause four distinct autosomal dominant muscle diseases. Neurology 2004;62:538-543.
2. Burns RJ, Bretag AH, Blumbergs PC, Harbord MG. Benign familial disease with muscle mounding and rippling. J Neurol Neurosurg Psychiatry 1994;57:344-347.
3. Minetti C, Sotgia F, Bruno C, Scartezzini P, Broda P, Bado M, et al. Mutations in the caveolin-3 gene cause autosomal dominant limb-girdle muscular dystrophy. Nat Genet 1998;18:365-368.
4. Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, et al. The human gene mutation database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet 2020;139:1197-1207.
5. Straub V, Murphy A, Udd B, Corrado A, Aymé S, Bönneman C, et al. 229th ENMC international workshop: limb girdle muscular dystrophies-nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord 2018;28:702-710.
6. Gazzerro E, Sotgia F, Bruno C, Lisanti MP, Minetti C. Caveolinopathies: from the biology of caveolin-3 to human diseases. Eur J Hum Genet 2010;18:137-145.
7. Tsutsumi YM, Horikawa YT, Jennings MM, Kidd MW, Niesman IR, Yokoyama U, et al. Cardiac-specific overexpression of caveolin-3 induces endogenous cardiac protection by mimicking ischemic preconditioning. Circulation 2008;118:1979-1988.
8. Nixon SJ, Wegner J, Ferguson C, Méry PF, Hancock JF, Currie PD, et al. Zebrafish as a model for caveolin-associated muscle disease; caveolin-3 is required for myofibril organization and muscle cell patterning. Hum Mol Genet 2005;14:1727-1743.
9. Berling E, Verebi C, Venturelli N, Vassilopoulos S, Béhin A, Tard C, et al. Caveolinopathy: clinical, histological, and muscle imaging features and follow-up in a multicenter retrospective cohort. Eur J Neurol 2023;30:2506-2517.
10. Maki T, Matsumoto R, Kohara N, Kondo T, Son I, Mezaki T, et al. Rippling is not always electrically silent in rippling muscle disease. Muscle Nerve 2011;43:601-605.