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Letter to the Editor

Caveolinopathy Due to the c.80G>A Variant in the CAV3 Gene, Presenting with Hyper-CK-Emia and Pseudohypertrophy, is Indicative of Myopathy

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We read with interest the article by Akbulut *et al.* regarding a previously healthy 15-year-old male patient who presented with vomiting and markedly elevated creatine-kinase and troponin levels, raising suspicion of acute myocarditis ^[1]. However, cardiac magnetic resonance imaging (cMRI) revealed non-ischemic myocardial fibrosis and non-compaction morphology, also known as left ventricular hypertrabeculation (LVHT), and genetic testing identified a pathogenic de novo variant in the CAV3 gene consistent with rippling muscle disease (RMD) ^[1]. While the study is informative, it warrants further discussion.

A first point is that the unremarkable electromyography (EMG) finding is surprising ^[1]. Given that the patient clearly had a skeletal muscle myopathy ^[1], one would have expected needle EMG to show either an absence of electrical activity due to the replacement of active muscle tissue with fibrous/fatty tissue or a myopathic pattern within the active muscle tissue. Was needle EMG actually performed on the patient, or was the examination limited to testing for myasthenia? What is meant by the "myasthenia protocol"? Was only repetitive nerve stimulation used?

A second point is that no muscle MRI (mMRI) was performed to determine whether fibrosis or fatty replacement was present in the muscles. Since the patient exhibited calf hypertrophy, and calf hypertrophy often actually represents pseudohypertrophy, it is conceivable that mMRI would have revealed atrophy or fibrosis of the affected muscles. Muscle fibrosis can be detected on mMRI using T1- and T2-weighted images; Furthermore, knowledge of the distribution of the affected muscle is important. Abnormal mMRI findings in patients with the CAV3 variant c.80G>C have previously been reported ^[2].

Third, no muscle biopsy was performed on the patient ^[1]. While muscle biopsy findings in RMD can be unremarkable, mild to moderate dystrophic changes, variation in muscle fiber size, degenerating and regenerating fibers, and an increase in centrally located nuclei are frequently observed ^[3]. Replacement of muscle tissue by adipose tissue is occasionally seen ^[3]. Immunohistology may reveal a marked reduction or absence of caveolin-3 at the muscle fiber membrane, leading to the structural disintegration of caveolae ^[3]. Immunohistochemistry typically shows a mosaic-like or diffusely reduced immunosignal at the membrane, and Western blot analysis demonstrates a reduced total amount of caveolin-3 ^[3].

The fourth point is that there was no report as to whether or not the index patient exhibited the phenomenon of "rippling muscles" ^[1]. This phenomenon manifests not only clinically (rapid muscle contractions occurring spontaneously or triggered by percussion) but is also detectable via needle electromyography (EMG) ^[4]. On EMG, "rippling" appears as bursts of brief, low-amplitude spikes resembling discharges from individual muscle fibers ^[4]. If the patient did not exhibit "rippling muscles," he should not be classified as RMD.

Fifth, "late gadolinium enhancement" (LGE) is not necessarily attributable to CAV3-associated cardiomyopathy but can also be a feature of LVHT ^[5]. Did the extent of the LGE increase during the 18-month follow-up period? Normal cardiac function throughout the entire period suggests that the LGE finding remained stable during the follow-up period.

Finally, the cause of the vomiting should be explained, and it should be clarified whether cMRI revealed any abnormalities other than LVHT and LGE.

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