A case of an Anoctamine 5 (ANO5) Muscle Disorder presenting with an asymptomatic hyperCKemia phenotype

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ICNC 2024 Footprints to the future
INTERNATIONAL CHILD NEUROLOGY CONGRESS
Cape Town, South Africa I May 6-10, 2024

OBJECTIVES

Asymptomatic hyperCKemia is defined, as the presence of serum creatine kinase (CK) values beyond 1.5 times the upper limit of normal for age, race and sex in patients without muscle-related symptoms.(1) Asymptomatic hyperCKemia is a laboratory finding that may occur in association with many neuromuscular or non-neuromuscular conditions, and may be the earliest sign of some neuromuscular diseases. For example, in the 2-year cohort study by Rubegni et al. (2019), an underlying genetic neuromuscular cause was identified in 14 of 34 patients with asymptomatic hyperCKemia.(2)

Here, we aimed to present an asymptomatic case in which CK elevation was discovered incidentally while investigating the etiology of transaminase elevation and a homozygous pathogenic mutation in the ANO5 gene was detected in the etiology.

CASE PRESENTATION

An eight-year-old girl patient, who was investigated by pediatric gastroenterology for the etiology of minimal transaminase elevation detected during routine check-up, was consulted to our department upon detection of elevated CK. She was born of second-degree consanguineous parents, after an uneventful pregnancy, by emergency cesarean section due to preeclampsia at 32nd gestational week with 1500g birth weight. She had no clinical complaints and her developmental milestones were compatible with her age. Her anthropometric measurements and physical and neurological examinations were normal. Her serum CK values were 2536, 1653, 2896 and 1696 IU/L, respectively. Gastroenterologic and metabolic examinations revealed no pathologic findings suggestive of any specific gastroenterologic or metabolic disease. Electroneuromyographic and echocardiographic tests were normal. The MLPA analysis of the Duchenne Muscular Dystrophy (DMD) gene was normal. In the neuromuscular diseases gene panel, a homozygous splice donor mutation [c.1898+1G>A (p.Met470LeufsTer16)] in the Anoctamine 5 (ANO5) gene was detected, and the patient was diagnosed with the asymptomatic hyperCKemia phenotype of ANO5-related muscle diseases.

DISCUSSION

ANO5 gene is located at 11p14.3 chromosome region and encodes anoctamin 5 (ANO5), which is highly expressed in skeletal muscle, cardiac muscle, chondrocytes and osteoblasts.(3) ANO5 is located in intracellular vesicles and the sarcoplasmic/endoplasmic reticulum. It functions as a sarcoplasmic/endoplasmic reticulum-associated putative intracellular Ca^{+2}-activated chloride channel and plays a role in cell membrane fusion and repair.(3,4)

Anoctaminopathy-5 is a group of clinically heterogeneous disorders due to autosomal dominant or recessive mutations in ANO5.(3) In the literature, more than 120 mutations linked to hereditary skeletal muscle or bone disorders in ANO5 have been identified.(3) Monoallelic (AD), gain-of-function mutations in ANO5 cause a rare skeletal disorder characterized by bone fragility and abnormalities in facial and tubular bones, termed gnathodiaphyseal dysplasia, and biallelic (AR), loss-of-function mutations cause a wide spectrum of muscle disorders.(3,4) ANO5-related muscle disorders has four phenotypes: limb-girdle muscular dystrophy type R12, Miyoshi distal myopathy type 3, metabolic myopathy-like (pseudometabolic) phenotype, and asymptomatic hyperCKemia, as in our case.(4) Asymptomatic hyperCKemia may be the first sign of ANO5-related muscle disorders and may transform into other muscle phenotypes over time.(3)

In conclusion, neuromuscular disorders are a group of diseases with an extremely broad phenotypic spectrum. Even in asymptomatic cases, in the presence of persistently elevated serum transaminase and creatine kinase levels, neuromuscular disorders should be kept in mind in etiological investigations.

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