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RHABDOMYOLYSIS AS AN UNCOMMON MANIFESTATION OF ANOCTAMIN-5 MUSCULAR DYSTROPHY

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ABSTRACT

Background: Anoctamin-5 (ANO5) muscular dystrophy is a rare neuromuscular disease. Muscular weakness and impaired gait may be evident at the moment of diagnosis, serving as defining characteristics of additional muscular dystrophies. Rhabdomyolysis, on the other hand, is a rare presentation Understanding this phenotype is of great importance since it can go unnoticed by physicians, leading to misdiagnosis of metabolic myopathies or delayed diagnosis. We discuss a case of recurrent rhabdomyolysis due to ANO5 muscular dystrophy.

Case Report: A 34-year-old man was referred to our Reference Centre for Hereditary and Metabolic Diseases due to incidentally elevated creatine kinase levels of 4369 U/l (normal value: < 171 U/l) in the context of acute renal colic. He described a 10-year history of progressive myalgia induced by physical activity, particularly in the lower extremities, muscle spasms, and sporadic reddish to brown urine. Although no muscle weakness was detected upon neurological examination, bilateral calf hypertrophy was noted. A comprehensive laboratory analysis was conducted to exclude acquired causes of rhabdomyolysis, including electrolyte abnormalities, endocrine disruptions, and autoimmune myopathies. Considering the high suspicion of an inherited aetiology, we proceeded with next-generation sequencing of rhabdomyolysis-related genes. Genetic testing revealed a c.1180+6t>Cp homozygous mutation in ANO5 gene, which confirmed anoctamin-5 muscular dystrophy.

Conclusions: ANO5 muscular dystrophy is a rare cause of inherited rhabdomyolysis. Understanding this phenotype is crucial for accurate and timely diagnosis. Currently, there is no specific treatment for this condition, but management should include avoiding heavy muscle training and use of statins.

KEYWORDS

Rhabdomyolysis, muscular dystrophies, metabolic myopathies

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LEARNING POINTS

- Anoctamin-5 (ANO5) muscular dystrophy is a rare neuromuscular disease originated by homozygous mutations in ANO5, a gene encoding a protein with the same name located on chromosome 11. ANO5 is a calcium-activated chloride channel that is highly expressed in heart and skeletal muscle. It is a rare cause of inherited rhabdomyolysis. Understanding this phenotype is crucial for accurate and timely diagnosis.
- We must emphasize how meticulous medical history taking along with a high index of suspicion are essential to diagnose this disease.
- Currently, there is no specific treatment for this condition, but management should include avoiding heavy muscle training and use of statins.

INTRODUCTION

Although consensus on the diagnostic criteria is lacking, rhabdomyolysis can be defined as a life-threatening syndrome characterized by acute onset of muscle weakness, myalgia, and myoglobinuria, along with an elevation of serum creatine kinase (CK) levels to at least five times the upper normal limit or a CK cut-off value of greater than 1000 IU/l. Surprisingly, the classical triad of symptoms is uncommonly seen[1]. HyperCKemia is a term used to describe a chronic elevation of serum CK in patients with no clinical and histopathological evidence of neuromuscular disease[2].

The association between rhabdomyolysis and metabolic myopathies is more often recognized in clinical practice than its association with muscular dystrophies, which is described as pseudometabolic phenotype, defined by exercise intolerance, myalgia with or without recurrent rhabdomyolysis[3-5].

Numerous etiologic factors can lead to rhabdomyolysis, namely strenuous or unaccustomed physical exercise, drugs, toxins, infections, ischaemia, endogenous triggers (both hyperthyroidism and hypothyroidism), trauma, compartment syndrome, prolonged immobilization, heat exposure or hyperthermia of any cause, convulsive seizure, burn injury and electrocution. Importantly, most of the patients experience their first episode due to an acquired cause, that often requires no further diagnostic evaluation. Conversely, inherited aetiologies should be considered in the following conditions: recurrent rhabdomyolysis, family history of rhabdomyolysis, rhabdomyolysis provoked by minimal exertion, fever and fasting, symptoms such as muscle spasms, limb weakness, muscle hypertrophy or atrophy and hyperCKemia between attacks. Strikingly, the aetiology of recurrent rhabdomyolysis remains unknown in nearly 60% of patients and muscular dystrophies are often not considered during diagnostic workups in such patients[4].

CASE DESCRIPTION

A 34-year-old man was referred to our Reference Centre for Hereditary and Metabolic Diseases due to incidentally elevated CK levels of 4369 U/l (normal value: < 171 U/l) detected after an acute renal colic. The patient's past medical history included significant alcohol and tobacco abuse. He was born into a consanguineous family. He described a 10-year history of progressive myalgia induced by physical activity, particularly in the lower extremities, muscle spasms, and sporadic reddish to brown urine. Although no muscle weakness was detected upon neurological examination, bilateral calf hypertrophy *(Fig. 1)* and muscle atrophy in the right lower limb *(Fig. 2)* were noted. His son, with 11 years old, had begun seeing a neurologist due to related symptoms, namely myalgia and elevated CK levels.

A comprehensive laboratory analysis was conducted to exclude acquired causes of rhabdomyolysis, including electrolyte abnormalities, endocrine disruptions, and autoimmune myopathies. Magnetic resonance imaging (MRI) of the thighs identified adipose degeneration in lower limbs



Figure 1. Bilateral calf hypertrophy.



Figure 2. Muscle atrophy in the right lower limb.

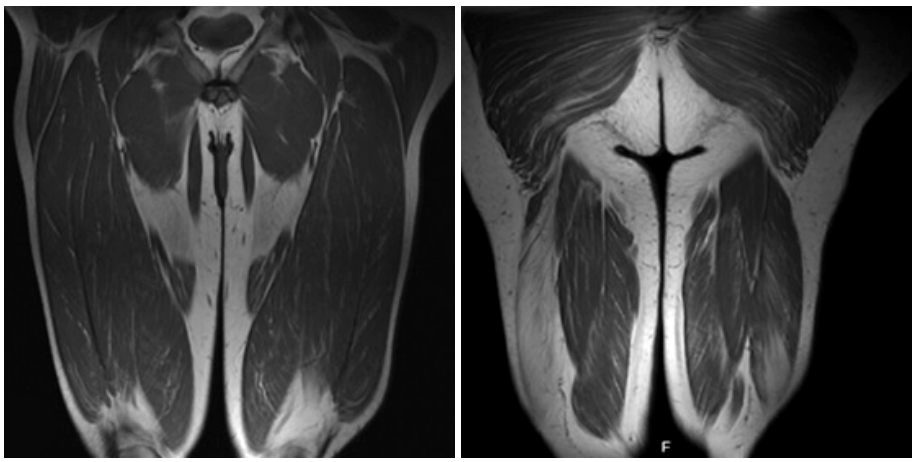


Figure 3. Magnetic resonance imaging of the thighs. Coronal view from T1 and T2 weighted sequences with fat suppression showing A) normal muscle structure and B) fatty degenerative changes in long adductor and the long portions of the femoral biceps, especially on the right.

(Fig. 3). Electromyography findings were consistent with fibrillation potentials and positive sharp waves. Considering the high suspicion of an inherited aetiology, we proceeded with next-generation sequencing of rhabdomyolysis-related genes. Genetic testing revealed a c.1180+6t>Cp homozygous mutation in the anoctamin-5 (ANO5) gene, which confirmed ANO5 muscular dystrophy.

Currently, there is no specific treatment for this condition. Therefore, managing these patients requires symptomatic and supportive strategies. Pain was successfully managed with tapentadol. Magnesium was prescribed to relieve cramps. Due to cyanocobalamin deficiency oral supplementation was started. The patient was advised to keep a program based on rest, hydration, and analgesia. His symptoms improved, however his CK values remained elevated, ranging from 1436 to 5502 U/l. The patient maintains regular follow-up in our Reference Centre for Hereditary and Metabolic Diseases. Clinical evaluations indicate symptom improvement, and periodic laboratory analyses show a chronic elevation of serum CK. An echocardiogram was performed, revealing no abnormalities.

DISCUSSION

The causes of recurrent episodes of rhabdomyolysis include inherited metabolic diseases, genetic disorders of the skeletal muscle and autoimmune disorders *(Table 1)*[6]. Recurrent episodes of rhabdomyolysis should prompt workup to identify underlying defects in muscle metabolism[5-7].

Metabolic myopathies			Muscular dystrophies	Congenital myopathies	Autoimmune disorders
Glycogen storage diseases	Disorders of lipid and fatty acid oxidation	Mitochondrial disorders			
McArdle disease (mutations in PYGM gene)	Carnitine transport system disorders	Complex I, II, III, IV, tRNA mutations, DGUOK	Dystrophinopathy (Duchenne and Becker)	RYR1-myopathy	Dermatomyositis
Cori disease (glycogen debranching enzymes deficiency)	Long-chain fatty acid oxidation disorder		Anoctaminopathy		Polymyositis
Tarui disease (phosphofructokinase deficiency)	Short and medium-chain acyl-coenzyme A dehydrogenase deficiency		Caveolinopathy		
	Glutaric aciduria type 2		Dysferlinopathy		
	LPIN1-myopathy		FKRP-opathy		
			Sarcoglycanopathy		

Abbreviations: DGUOK, deoxyguanosine kinase gene; FKRP, fukutin-related protein gene; PYGM, glycogen phosphorylase muscle associated; LPIN1, phosphatidic acid phosphatase deficiency; RYR1, ryanodine receptor 1 gene.

Table 1. Rare causes of recurrent rhabdomyolysis.

	Baseline CK levels	Muscle strength
Muscular Dystrophies	Highly elevated between attacks	Fixed weakness
Metabolic Myopathies	Normal or minimally elevated*	Normal between attacks**

* Except for patients with glycogen storage diseases.
** May develop fixed weakness at the advanced stage of the diseases.

Table 2. Differences in creatine kinase levels and muscle strength: muscular dystrophies vs metabolic myopathies[4,5].

This case underlines the role of ANO5 in the diagnostic pathway of myalgia and rhabdomyolysis as we describe a patient presenting with a metabolic myopathy-like phenotype who was found to have an ANO5 variant after testing with a custom designed neuromuscular genetic panel. Recessive mutations in ANO5 are responsible for a continuum of four clinical phenotypes: limb girdle muscular dystrophy type R12 (LGMDR12), Miyoshi distal myopathy type 3 (MMD3), metabolic myopathy-like (pseudometabolic) and asymptomatic hyperCKemia. The main clinical presentation is LGMDR12, patients typically develop pelvic girdle weakness followed by an involvement of the shoulder girdle musculature and asymmetrical muscular atrophy. In MMD3 patients initially develop asymmetric weakness and atrophy of calf muscles. The metabolic myopathy-like phenotype can mimic, overlap with or convert to the classic manifestations of metabolic myopathies[3].

The fear of further muscle damage from physical activities may discourage patients from exercising, leading to a sedentary lifestyle and obesity. Hence, it is essential to promote weight control and mobility. Moderate intensity aerobic exercise has been shown to improve cardiovascular fitness, but it must be performed under professional supervision to avoid an overexertion that may trigger rhabdomyolysis. Patients must be instructed to avoid heavy muscle force training and the use of statins. We suggest improving patient follow-up by assessing muscle strength and functional status every 6 months. Cardiac findings include dilated cardiomyopathy and arrhythmias; hence all patients should undergo periodic echocardiography and 24-hour Holter monitoring. Although respiratory muscle involvement is rare, patients with respiratory symptoms should undergo pulmonary function testing[8]. Management of these patients must include genetic counselling. Carrier testing for at-risk family members, prenatal diagnosis for a pregnancy at increased risk and preimplantation testing are possible if the pathogenic variants in the family have been identified. Finally, patient education is imperative to avoid potential triggers in the long term[3]. Muscle biopsy is not mandatory but usual findings are consistent of necrotic myofibers and amyloid deposits[5,9].

We aim to highlight the importance early detection of rhabdomyolysis in the workup of muscular dystrophies. The presence of weakness and the highly elevated CK levels between attacks is a hallmark of muscular dystrophies *(Table 2)*. In a retrospective study with 475 patients with rhabdomyolysis, muscular dystrophy was suspected in only 1 patient. Immunohistochemical studies of muscular dystrophy/rhabdomyolysis-related proteins must be considered in patients with negative biochemical studies for metabolic myopathies[5].

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