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Recurrent rhabdomyolysis as a presenting feature of glycogenosis IX (GSD IX): a case report

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ABSTRACT

Rhabdomyolysis is the clinical picture characterized by the destruction of skeletal muscle. It is associated with the consequent elevation of serum creatine kinase above five times its standard value or greater than 1,000 U/L.

Its most frequent causes are acquired. However, less frequent causes, such as congenital metabolic diseases, should be considered when the rhabdomyolysis event recurs.

We describe the case of a pediatric patient with recurrent rhabdomyolysis, which triggered by a type IX glycogenosis with a *PHKA1* gene mutation.

This pathogenic variant generates muscle phosphorylase kinase enzyme deficiency, hindering the use of glycogen as an energy source during prolonged fasting or metabolic demands.

We consider it essential to increase knowledge about these entities in the face of recurrent rhabdomyolysis in the pediatric age for early detection and timely referral to a specialist.

Keywords: *glycogenosis IX; rhabdomyolysis; phosphorylase kinase;* PHKA1 *gene.*

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INTRODUCTION

Rhabdomyolysis is a clinical entity characterized by the destruction of skeletal muscle and the massive release of intracellular contents into the extracellular compartment, leading to systemic complications.[1,2]

The most frequent clinical presentation consists of myalgia and muscle weakness associated with elevated serum creatine kinase (CK) levels above five times the normal value or greater than 1,000 IU/L.[1,2]

Among the etiologies described, the most frequent are acquired, including infections (approximately 30% of cases), trauma, and drugs as the foremost exponents. Congenital disorders leading to pathology are much less frequent. However, they predominantly affect the pediatric population in their first 10 years of life. They should always be suspected in the face of recurrent episodes of rhabdomyolysis with no other identifiable cause.[1-3]

This group includes congenital metabolic diseases, including beta-oxidation disorders, mitochondrial diseases, muscular dystrophies, and glycogen storage diseases.[1-4]

Glycogen storage diseases or glycogenosis are a group of hereditary metabolic diseases with variable clinical presentations. They share in their pathophysiology the alteration in different metabolic points of the glycogen pathway, which results in difficulty in its utilization as a source of glucose and its subsequent excessive accumulation, mainly at the hepatic and muscular levels. The approximate global incidence is estimated at 1 case per 20,000-43,000 live births.[4,5]

Glycogenosis type IX is caused by mutations in the enzyme phosphorylase kinase (PhK), which activates the enzyme phosphorylase, which catalyzes the cleavage of the terminal units in the glycogen chain. These mutations lead to inefficient glycogenolysis, with excessive hepatic and/or muscular glycogen storage.[4-6]

PhK is a heterotetramer consisting of α, β, δ (calmodulin), and γ subunits, all encoded by different genes that are predominantly expressed mainly at the hepatic, muscular, and brain levels. The *PHKA1* genes encode the α subunit of expression in skeletal muscle tissue and *PHKA2* of expression at the hepatic level. Both genes are inherited in an X-linked manner, so the pathology is more frequently expressed in males. Generally, there is usually a compatible family history in the maternal line.[3-5]

The spectrum of clinical presentation is vast depending on the mutations described and the organ primarily affected; the predominant signs and symptoms result from ineffective glycogenolysis. Muscular symptoms usually include mild to moderate hypotonia, weakness, myalgias, rhabdomyolysis, and, in some cases, delayed acquisition of maturational patterns of gross motor development has been described.[4-6]

This wide variability in its symptomatology makes glycogenosis type IX an underdiagnosed disease.[5]

We present the case of an 11-year-old patient diagnosed with glycogenosis type IX after recurrent rhabdomyolysis in the context of infectious intercurrences. This work aims to increase the knowledge about these pathologies in our environment.

CLINICAL CASE

An 11-year-old previously healthy male patient presented with a recent onset of fever associated with upper airway infection and intense pain in both lower limbs, particularly at the level of the calves, with functional impotence. Physical examination revealed pain in the palpation of both lower limbs. No visceromegaly was detected on abdominal palpation. Diuresis was preserved without choluria.

The laboratory showed a marked increase in CK (maximum value: 1,480 U/L) and alteration of the hepatogram with increased transaminases (aspartate aminotransferase [GOT] 103 U/L, alanine aminotransferase [GPT] 60 U/L). Given the suspicion of myositis of viral etiology, serologies for cytomegalovirus, Epstein-Barr virus, dengue, and parvovirus were performed with negative results. Outpatient treatment was indicated with frequent controls, abundant oral hydration, and symptomatic treatment. The condition resolved *ad integrum*.

In the following two years, he presented two new episodes, always in a febrile context and with similar clinical characteristics (maximum CK of 2560 U/L, GOT 103 U/L, GPT 47 U/L), without requiring hospitalization. Upon questioning, his parents reported that, when performing intense physical exercise, the patient presented pain in both lower limbs, even with the need to stop the activity momentarily.

In the case of a patient with recurrent episodes of rhabdomyolysis, with increased CK and transaminases, in the face of triggers such as increased metabolic demands due to fever or

exercise and without an etiopathogenic diagnosis, it was decided to consult the Inborn Errors of Metabolism Service of our institution.

The patient was evaluated, and based on his pathological history, acylcarnitines, carnitine, and amino acids were determined in blood, all within normal parameters, and urinary organic acids, which showed minimal non-significant alterations.

As clinical suspicion persisted, studies were extended with an expanded genetic panel for rhabdomyolysis, which reported the c.1663C>T variant in hemizygosis in the X-linked *PHKA1* gene encoding for muscle-expressing PhK, which is deficient in glycogenosis IX.

The patient started follow-up with a specialty and initiated nutritional and preventive control measures, such as having up-to-date vaccinations, maintaining adequate hydration, and avoiding strenuous physical exercise. The patient was also instructed to consult during episodes of muscle pain or choluria and was given a crisis letter to present to the healthcare personnel.

DISCUSSION

Rhabdomyolysis in children is a diagnostic challenge for the treating physician. The presence of infectious entities, particularly viral, can cause the lytic phenomenon itself or act as a "trigger" in patients with undiagnosed metabolic disorders, making diagnosis difficult.

In the face of recurrent episodes of rhabdomyolysis, mainly in those triggered by increased metabolic demands, we consider it essential to broaden the diagnostic horizon after having ruled out the most frequent entities. The timely identification of these disorders has favorable prognostic implications.[1,2,5]

Among the causative congenital entities of recurrent rhabdomyolysis in children are fatty acid beta-oxidation disorders, e.g., carnitine palmitoyl transferase II (CPT2) deficiency, and glycogen storage diseases such as glycogenosis V or McArdle's disease. Some mitochondrial diseases and muscular dystrophies are also included in this group.[1-3,5] Mutations in the *LIPIN1* gene should be considered because they are a relatively frequent cause of rhabdomyolysis in pediatrics,[7] and TANGO 2 encephalopathy can be associated with episodes of rhabdomyolysis and other manifestations similar to mitochondrial diseases.[8]

Once the most common causes of rhabdomyolysis have been ruled out, specific general laboratory tests can guide the diagnosis, for example, hepatogram, lactate dehydrogenase, uric acid, fasting blood glucose, ammonium, lactic acid, and lipidogram. Specific metabolic studies determine acylcarnitines, carnitine, and amino acids in blood and urinary organic acids. These results may guide the diagnosis, which molecular studies can confirm, or they may be normal, and molecular studies also continue the etiological search, generally gene panels or nuclear exome studies.

Muscle biopsy can be used for enzymatic and genetic analysis in case of negative tests with high clinical suspicion.[1,2,4,5]

Our patient presents a rare variant in the hemizygous form in the *PHKA1* gene that is predicted to be pathogenic in silico. It is present in hemizygous form 1 among about 34,000 male individuals from worldwide population banks and has not been previously described.

The pathogenic variants in *PHKA1* cause a deficit of the PhK enzyme predominantly at the muscular level. Our patient's clinical presentation is mainly characterized by episodes of recurrent rhabdomyolysis in the context of increased metabolic demands.

There is scarce literature regarding the long-term treatment of this pathology and its natural evolution.

The follow-up of these patients should be interdisciplinary. The main goal of treatment is adequate metabolic management to prevent associated complications.[4,5] ■

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