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Metabolic vs inflammatory myopathy: diagnostic difficulties and errors in myopathies – case report

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ABSTRACT

Glycogen storage diseases are genetic metabolic disorders of glycogen metabolism. There are more than 12 types and they are grouped based on the enzyme deficiency and the affected tissue.
We present the case of a 43-year-old female with glycogen storage disease type III with liver, skeletal and cardiac muscle involvement whose disease was misdiagnosed with idiopathic inflammatory myopathy and treated with glucocorticoids. Glucocorticoids are an inadequate therapy for this metabolic myopathy and they interfere with the carbohydrate metabolism causing more glycogen storage in the liver.

Keywords: myopathy, glycogen storage disease, glucocorticoids

INTRODUCTION

Glycogen storage diseases are systemic, inherited metabolic disorders of glycogen metabolism. There are over 12 types and they are grouped based on the enzyme deficiency and the affected tissue. Glycogen storage disease type III is a disorder of glycogenolysis due to AGL gene mutations causing storage of limited dextrin in the liver and muscles due to glycogen debranching enzyme deficiency. The diagnosis is made by demonstrating enzyme deficiency in the liver or muscle or by genetic test showing AGL gene mutation. There is no specific treatment for this type of GSD. The dietary treatment is used to maintain normoglycemia.

CASE REPORT

We present the case of a 43-year-old female patient who was referred to the rheumatology department for symmetric proximal muscle weakness and myalgia with an insidious onset over the last year.

From her medical history we mention a hepatic glycogen storage disease with hepatomegaly and recurrent episodes of hypoglycemia diagnosed in her early childhood (no documents available) and non-obstructive hypertrophic cardiomyopathy diagnosed in 2016 by cardiac MRI with recurrent angina (normal coronary angiography).

The patient presented for the first time in another rheumatology service in October 2018 with bilateral proximal muscle weakness. Laboratory data revealed normal inflammatory markers, serum muscle enzymes elevation (CK=350 UI/l, LDH=250 UI/l), low glycated hemoglobin (HbA1C = 4.75%) and thyroid function tests within normal ranges. Serological studies revealed negative ANA, negative ANCA and negative antiJo1 autoantibodies. The electromyography (EMG) showed proximal myopathy features and the muscle biopsy revealed increased concentrations of glycogen with minimal mononuclear cell infiltration. Based on these investigations the patient was diagnosed with polymyositis and corticotherapy was initiated (methylprednisolone 32 mg per day) with no clinical improvement.

Six months later, the patient was admitted to our rheumatology department with no significant clinical improvement despite her daily dose of 32 mg methylprednisolone. Upon admission she had symmetric, proximal reduced muscle strength and pain at active mobilization of the extremities; otherwise, physical examination within normal limits. Laboratory data showed inflammatory markers within nor-

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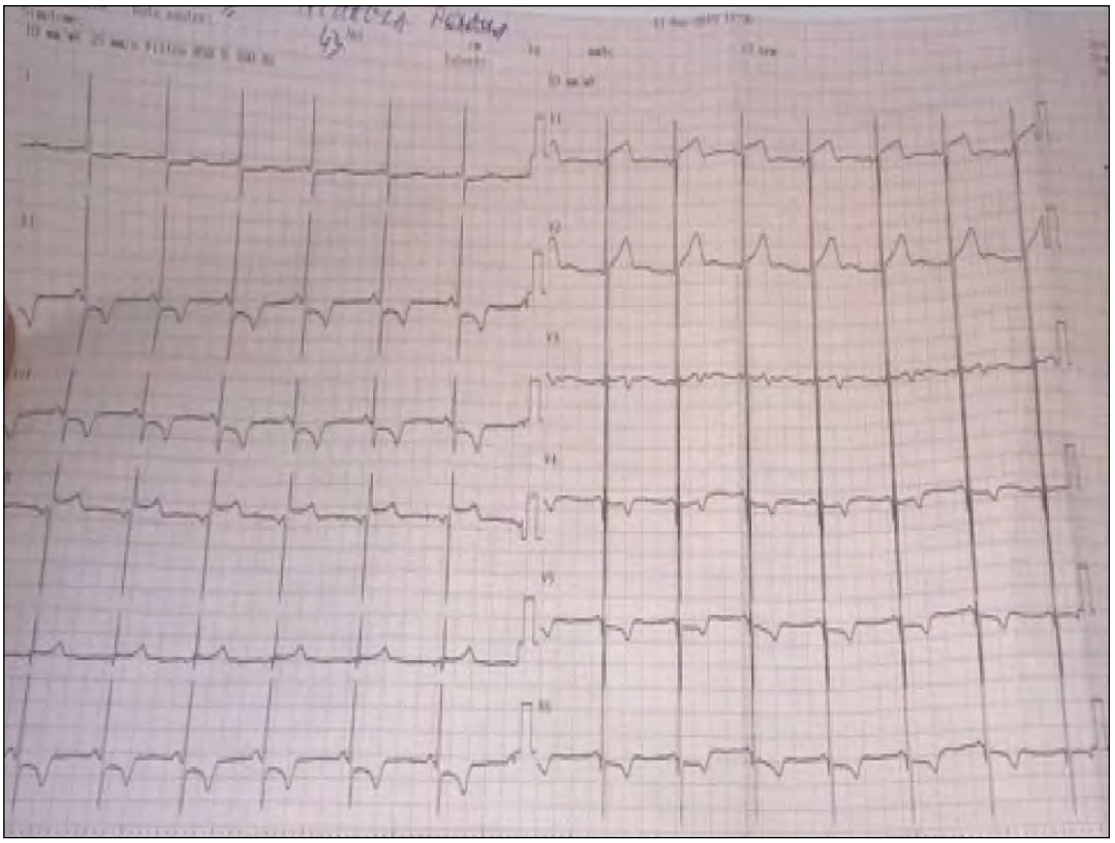

FIGURE 1. *The patient electrocardiogram*

mal ranges, increased serum muscle and cardiac enzymes (CK x 2 ULN, CK-MB x 3 ULN, troponin I x 10 ULN, ALT x 4 ULN, AST x 2 ULN) and minimal cholestatic syndrome (GGT x 2 ULN). The electrocardiogram showed left ventricular hypertrophy with secondary repolarization changes.

The cardiac ultrasound showed non-dilated left ventricular with concentric hypertrophy with normal systolic function, longitudinal left ventricle disfunction and pseudonormal diastolic function, moderate left atrium dilatation, right atrium and ventricle within normal ranges, moderate mitral regurgitation.

The abdominal ultrasound showed a slightly hyperechoic enlarged liver.

The differential diagnosis of the muscle weakness took into consideration a neuromuscular disorder which was ruled out by the EMG. Also, an infectious myopathy was excluded (no signs or symptoms of infection, normal inflammatory markers, negative tests for trichinosis, toxoplasmosis, and cysticercosis). Regarding the patient's previous diagnosis of polymyositis, the ACR/EULAR 2017 classification criteria for idiopathic inflammatory myopathies (IIM) aren't met - probability of IIM 8%.

So, considering the normal values of the inflammatory markers, the lack of clinical response to glucocorticoids, the myopathic EMG and the muscle biopsy which revealed glycogen accumulation in the myocytes and the patient's medical history - hepatic glycogen storage disease, the diagnosis was *metabolic myopathy in the context of a glycogen storage disease.*

A liver biopsy was performed to confirm the diagnosis of glycogen storage disease and it showed: conserved lobular architecture, normal portal spaces without fibrosis or inflammatory cell infiltration, diffuse distension of hepatocytes with a mosaic pattern, hepatocytic PAS positive inclusions - intracytoplasmic glycogen accumulation consistent with the diagnosis of glycogen storage disease.

Also, the left ventricular hypertrophy with recurrent angina with normal coronary arteries (coronarography) and increased levels of troponin were interpreted in the context of glycogen storage in the cardiac muscle with slow, persistent release of cardiac enzymes

The differential diagnosis of the type of glycogen storage disease took in consideration the types with muscle and liver involvement. These are GSD type II (Pompe disease), GSD type III (Cori Forbes) and GSD type IV (Andersen) [1]. Only glycogen storage disease type II has specific treatment - enzyme re-

placement therapy [2]. So, first excluded this type by testing the level of alfa-1,4-glucosidase which was within normal ranges. Considering the features and the poor prognosis of GSD type IV - most children die by age 2-5 years [3], the diagnosis was considered GSD type III. There are 2 subtypes: GSD type IIIA with muscle and liver involvement and GSD type IIIB only with liver involvement [1].

In the light of this diagnosis, glucocorticoids are an inadequate therapy and they interfere with the carbohydrate metabolism causing more glycogen storage in the liver. So, we decided to gradually withdraw corticotherapy. The only treatment for GSD type III is dietary and it includes uncooked cornstarch (1-3g/kg three times daily) to maintain euglycemia and high protein diet (3g/kg) to provide a substrate for gluconeogenesis [4]. Regarding the hypertrophic cardiomyopathy and the recurrent angina, we recommended a low dose of beta blocker to reduce the heart rate thereby reducing the work of the heart and its need for oxygen.

The prognosis for GSD type III is variable and it depends on the cardiac and hepatic complications: liver failure, hepatocarcinoma, heart failure, malignant arrhytmias due to fibrosis [1].

DISCUSSIONS

Glycogen storage diseases are systemic disorders with defective glycogenolysis caused by various enzyme defects. There are 12 types of GSD (Table 1).

GSD type III is also known as Cori-Forbes disease in honor of Cori who in 1952 described the abnormal structure of GSD III glycogen and Forbes who in 1953 linked the symptoms of the disease to the abnormal glycogen structure. It is an autosomal recessive caused by mutations in the AGL gene that result in glycogen debranching enzyme (amylo-1,6-glucosydase, 4-α-glucantransferase enzyme) deficiency leading to limited dextrin accumulation in tissues [4]. The overall incidence of this disorder is 1:100,000 [5,6,7].

Phenotypically, Cori's disease can be classified into GSD type IIIa (85%) with involvement of the liver, heart and skeletal muscle and GSD type IIIb in which only the liver is affected (15%) [7].

There are also described two other subtypes – GSD IIIc presumably the result of deficiency of only glucosidase debranching activity and GSD IIId presumably the result of deficiency of only transferase debranching activity. These 2 subtypes are extremely rare [5].

The typical clinical presentation of GSD IIIa consists of liver disease, myopathy and hypertrophic cardiomyopathy [8].

The onset of the disease is in infancy with hepatomegaly, hyperlipidemia, elevated hepatic transaminases and hypoglycemia [8]. Our patient described this clinical picture in the early childhood. In adolescence and adulthood the liver manifestations seem to regress and most patients have minimal signs of liver disease as we see in our patient too, possibly due to decreased glucose demands. Also, a growth retardation may occur [9].

In adulthood, the predominant symptom is muscle weakness affecting the extremities. Some patients as our patient show elevated levels of CK. Also, neuropathy may appear caused by the glycogen accumulation in axons [5].

Hypertrophic cardiomyopathy occurs in most patients with GSD IIIa, but it is mostly asymptomatic. There have been reported cases of congestive heart failure and sudden death [9].

The diagnosis of GSD III is confirmed by gene testing - identification of biallelic AGL mutations. If this can't establish a diagnosis, the assessment of debranching enzyme activity in muscle or liver can be considered. Also, this test can be performed on fibroblasts [4].

There is no specific treatment for debranching enzyme deficit. The dietary therapy consists of frequent high-protein meals (45% carbohydrate, 25% protein, 30% fat) to offer a substrate for gluconeogenesis and uncooked corn starch before sleep to avoid hypoglycemia overnight. There are reports of muscle weakness improvement in patients with high-protein diet [6].

The International Study on Glycogen Storage Disease III is a multi-center cohort study on 175 patients that revealed the most severe complications of GSD III: hepatic complications with an overall prevalence of 11% (adenomas and hepatic cirrhosis that in some cases leads to hepatocellular carcinoma), cardiomyopathy with a prevalence of 15% and muscle weakness with a prevalence of 34%. Also, cardiomyopathy was associated with a higher prevalence of distal myopathy [8].

Also, osteopenia and osteoporosis have been reported in GSD III and other glycogen storage disorders probably due to metabolic imbalance. In a study with 15 patients a significant proportion had BMD > 2 standard deviations below the mean value [10]. Similar results were obtained in other studies [11].

TABLE 1. *Glycogen storage diseases [1,4]*

GSD	Enzyme defect	Tissues	Clinical	Paraclinical	Diagnosis
Type 0	Glycogen synthase	Liver	Childhood onset Liver not enlarged Short stature Lethargy, nausea	Hypoglycemia Elevated blood lactate	Gene test Liver biopsy - decreased glycogen
Type I	Glucose-6-phophatase	Liver Kidney Neutrophils (Ib)	Childhood onset Tremors, lethargy, coma Short stature Hepatomegaly Enlarged kidneys Infections	Hypoglycemia Lactic acidosis Hyperlipidemia Hyperuricemia Proteinuria Neutropenia-Ib	Gene test Enzyme assay Liver biopsy - glycogen accumulation
Type II	Alpha-1-4-glucosidase (acid maltase)	All	Classic form - death in the first year Juvenile and adult form - heart failure, muscle weakness, dyspnea, variable prognosis	Elevated CK, ALT, AST, LDH Cardiomyopathy Respiratory insufficiency	Enzyme assay Gene test
Type III	Amylo-1-6-glucosidase	Liver Muscle	Childhood onset with hepatomegaly that regresses in adulthood Muscle weakness Fatigue	Elevated CK, ALT, AST Hypoglycemia Dyslipidemia Cardiomyopathy	Enzyme assay Gene test Liver biopsy
Type IV	Amylo-1,4 to 1,6-transglucosidase	Liver Muscle	Hepatosplenomegaly in the first 18 months of life Progresses rapidly Death between 3 and 5 years Rarely non-progressive	Elevated serum transaminases Cirrhosis	Enzyme assay Gene test Liver biopsy
Type V	Myopho-sphorylase	Muscle	Young adulthood onset Muscle weakness Myalgias	Transient myoglobinuria Elevated CK, LDH	Enzyme assay Gene test
Type VI	Liver glycogen phosphorylase	Liver	Hepatomegaly Growth retardation Benign course	Hypoglycemia Elevated ALT, AST Dyslipidemia	Enzyme assay Gene test Liver biopsy
Type VII	Phopho-fructokinase	Muscle	Muscle weakness Myalgias	Myoglobinuria Elevated muscle enzymes	Enzyme assay Gene test
Type VIII Type IX Type X	Phosphorylase activation defects (X-linked)	Liver	Hepatosplenomegaly Growth retardation Hypotonia Benign course	Hypoglycemia Hyperketosis Elevation of ALT, AST Dyslipidemia	Gene test
Type XI	Glucose transporter 2(GLUT2)	Liver Kidney	Hepatomegaly Growth retardation Dwarfism Moon-shaped face Fat deposition in the shoulders and abdomen	Hypoglycemia Ketonuria Dyslipidemia Hypophosphatemia Hyperaminoacidouria Glucosuria, galactosuria, proteinuria	Gene test Liver biopsy
Type XII	Aldolase A	Erythrocyte Muscle	Intellectual disability Muscle weakness Fatigue	Hemolytic anemia Elevated muscle enzymes	Enzyme assay Gene test

In the International Study on Glycogen Storage Disease III were described endocrinologic complications: 9% of patients were diagnosed with type 2 diabetes mellitus at median age 38 and 5 patients were diagnosed with polycystic ovaries [8].

Regarding the mortality, in this study, three patients died because of cardiac complications (cardiac fibrosis, congestive heart failure) at ages 1, 29 and 39 years. One patient aged 36 died because of liver failure in the context of hepatic cirrhosis and hepatocarcinoma [8].

CASE PARTICULARITY

It was presented the case of an adult female with proximal muscle weakness misdiagnosed as polymyositis and treated with methylprednisolone. The patient had an uncertain medical history with hepatomegaly and hypoglycemia in her childhood due to

a hepatic glycogen storage disease for which she didn't follow any diet. After muscle and liver biopsies, she was diagnosed with glycogen storage disease with skeletal muscle, liver and heart involvement. For the confirmation of the GSD type a genetic test will be performed to identify the AGL gene mutation.

CONCLUSIONS

Metabolic myopathies should be considered in the differential diagnosis of muscle weakness because glucocorticoids that are used for idiopathic inflammatory myopathy might be harmful in some metabolic disorders like glycogen storage diseases. There is no specific treatment for this systemic disorder. A multidisciplinary approach would be recommended to assess all complications and to establish the best medical and dietary therapy.

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