INTRODUCTION

Cori-Forbes disease or glycogen storage disease type III (GSDIII) caused by mutations in the AGL gene, that codifies amylo-1,6-glucosidase enzyme (1,2), this allows an accumulation of limit dextrin in liver, striated and cardiac muscles. GSDIII can be classified into IIIa, IIIb, IIIc, IIId. GSDIIIa is the most common (78%), targets liver, striated and cardiac muscle; IIIb affects 15% of patients and involves only the liver. Other cases with selective loss of glucosidase activity (IIIC) or transferase (IIId) add up to the remaining 7%.

GSDIII is biphasic, includes metabolic disorders with hepatomegaly in childhood, while after adolescence, myopathies develop (1). Complications like cirrhosis and hepatocellular carcinoma are less frequent (4). Definitive diagnosis is based on proving enzymatic deficiency (5), management includes a high dietary intake of protein with cornstarch supplementation (6). There is no cure, recommendations are based on symptoms follow-up and dietary treatment, whose compliance reflects positive results evidenced in normoglycemia (7).

It should be noted that GSDIII is a rare pathology, the overall incidence is 1/100 000 people and there is just a 25% chance of two brothers suffering this disease. Cases described here are remarkable due to the challenge that rare diseases pose in many countries when presented in association with other disorders and not as a particular group of entities.

CASE 1

A 7-years-old female patient, a native of Mérida, from the municipality of Monte Carmelo, Trujillo, Venezuela. In January of 2014, she is referred to pediatric gastroenterology consult in a university hospital “Dr. Pedro Emilio Carrillo” (HUPEC) due to a current disease of 10-month evolution characterized by an increase of abdominal circumference.

Firstborn child, birth weight: 3 000g; birth length: 50 cm. Healthy parents without close kinship. Physical exam reported weight: 12,2 kg, height: 75,5 cm. Soft, not-tender, and not-distended abdomen to palpation, with hepatomegaly, 7 cm below the costal margin. Liver span reports MEL (Midsternal line): 11cm., MCL (Midclavicular line): 10cm., AAL (Anterior axillary line): 8,5cm. Symmetrical and mobile extremities.
Paraclinical findings revealed: glycemia 49.3 mg/dL; cholesterol 213.20 mg/dL; HDL 18.40 mg/dL; VLDL 63.86 mg/dL; ALT 623.30 U/L; Alkaline phosphatase 686.80 U/L; Lactic dehydrogenase 1 085 UI/L; these values are noticeable for the magnitude of their alteration. An abdominal ultrasound showed compatible data with homogenous hepatomegaly, increased liver size could be observed, normal shape, homogenous echotexture with no focal or diffuse infiltrative lesions (Figure 1).

We prescribed diet therapy, based on the restriction of simple carbohydrates to be compensated with the administration of 2 measures of diluted cornstarch in a glass of water at 9:00 a.m. and 3:00 p.m. also 2½ measures at 1:00 a.m., 5:00 a.m., and 9:00 p.m. Consumption of moderate amounts of dairy, vegetables, and fruits.

Currently, the patient follows the recommendations, avoiding simple carbohydrates compensated with the administration of cornstarch. After 4 years of treatment, the physical exam reported hepatomegaly, weight: 20.5 kg, and size: 105 cm. (Figure 2.A.). Paraclinical exams show: Hb 10.7 g%, glycemia 40.9 mg/dL, urea 34.6 mg/dL, creatinine 0.5 mg/dL, cholesterol 154.90 mg/dL, HDL 23.10 mg/dL, LDL 81.06 mg/dL, VLDL 50.74 mg/dL, triglycerides 253.70 mg/dL, AST 416 U/L, ALT 303 U/L, these values reflect an improvement of the patient.

Subsequently, the patient is referred to the Centro de Atención Nutricional Infantil Antímano (CANIA), whose diagnosis was subclinical undernutrition, stunted, and glycogenosis. An evaluation was requested at the Instituto Venezolano de Investigaciones Científicas (IVIC), which showed the concentration of red-blood-cell glucose in the patient was 183 ug/g Hb and of her mother 110.9 ug/g Hb (N. V. 18-90 ug/g). Creatine kinase (CPK) in plasma of the patient was 37.0 U and of her mother 7.2 U (N.V. 4.3-29.8 U), confirming the GSDIII diagnosis. A risk of 25% of suffering the disease was established for future pregnancies.

CASE 2

5-year-old male patient, from Valera, in the municipality of Monte Carmelo, Trujillo, Venezuela. In October 2014 he attended a pediatric gastroenterology consultation at HUPEC for presenting an ongoing disease characterized by increased abdominal circumference.

Figure 1. Abdominal ultrasound shows homogenous hepatomegaly of case 1.

Figure 2. Current pictures of the patients. A. Case 1. B. Case 2.

CASE 2

5-year-old male patient, from Valera, in the municipality of Monte Carmelo, Trujillo, Venezuela. In October 2014 he attended a pediatric gastroenterology consultation at HUPEC for presenting an ongoing disease characterized by increased abdominal circumference.
Second gestation result, weight at birth: 2,700 g, length at birth: 49 cm. Apparently healthy parents with no close relatives. In its antecedents it stands out sister of 7 years (Case 1) who suffers from GSDIII.

Paraclinical findings revealed: Hb 9.20 g%; leukocytes 17 400 x mm3; glycemia 28.40 mg/dL; cholesterol 144.50 mg/dL and triglycerides 218.50 mg/dL. An abdominal ultrasound was performed, which reported a slight increase in size, increase in parenchymal ecogenicity, without dilation of the bile ducts; it could be concluded that the patient presented mild diffuse hepatic steatosis and discrete hepatomegaly 6 cm below the costal edge. The hepatometry referred LPE: 8 cm, LMC: 6.5 cm, LAA: 5.5 cm (Figure 3).

The patient is referred from HUPEC to CANIA with a diagnosis of glycogenosis and low height for age. In order to prevent hypoglycemia, dietary treatment is indicated based on the restriction of simple carbohydrates compensated by the intake of 2 measures of cornstarch diluted in a glass of water at 5:30 a.m., 3:00 p.m., 6:00 p.m., 9:30 p.m. and 1:30 a.m. The consumption of moderate amounts of dairy products, vegetables and fruits is allowed.

Subsequently, an appraisal is requested at the IVIC, where it was determined that the patient’s erythrocyte glycogen concentration was 458.7 ug/g Hb and that of the mother was 110.9 ug/g Hb (V.N 18-90 ug/g). Quantification of creatin kinase (CPK) in patient’s plasma was 20.0 U and mother’s was 7.2 U (N.V 4.3-29.8 U), confirming the diagnosis of GSDIII. It was established a risk of 25% of suffering the disease in future pregnancies.

In March 2018 the patient returns to consultation, the physical exam determines weight of 12.7 kg and height of 86 cm. Balloon-like abdomen, depressible, not painful on palpation, with hepatomegaly. Symmetrical and mobile extremities. Blood tests showed glycemia: 27.4 gr/dL; cholesterol: 188 mg/dL, H.D.L.: 29.8 gr/dL, L.D.L.: 99.9 mg/dL; AST: 219.20 U/L, ALT: 219.20 U/L. The mother reported administration of lesser doses of the treatment. The following controls show normoglycemia when the dietetic treatment is fulfilled. The most recent physical examination performed in November 2018 described weight: 13.8 kg; height: 87 cm; soft, non-painful abdomen with hepatomegaly (Figure 2.B.). The paraclinical analysis indicates Hb: 10.3 g%, Hto: 34%, platelets: 385 000 mm3, glycemia: 78 mg/dL.

**DISCUSSION**

Glycogenosis is an uncommon inherited disorder (8). In this study the cases correspond to GSDIII, the differential diagnosis is established with GSDVI, GSDIX, and mainly GSDI, since they have a delay in stature-ponderal growth, facies with round cheeks, hypoglycemia, and hepatomegaly. Unlike GSDI, GSDIII does not describe kidney disease, fasting ketosis is less prominent and transaminases are less high (9).

Diagnosis of GSDIII requires clinical and paraclinical studies. Physical examination is relevant to increase abdominal circumference by hepatomegaly, thin, short limbs, facies with round cheeks, low size for age (8), symptoms shown in both cases (Figure 2).

Enzyme deficiency disrupts glycogen degradation, which accumulates in vacuoles that hypertrophy hepatocytes (10). Poor hepatic glycogenolysis explains hypoglycemia and the vacular presence of glycogen leading to cytolysis, described in laboratory (paracli-
nical) analyses of cases under study such as increased transaminases and hyperlipidemia (3).

A metabolic imbalance could lead to osteopenia (11). Thus, in both cases, low size is reported for age placing below the 3rd percentile (12) according to World Health Organization (WHO) growth standards (13.14) (Figure 4 and 5).

In both cases, paraclinical analyses describe hypoglycemia and increased serum levels of triglycerides, cholesterol, CPK, AST, ALT, and bilirubin (8). They also reported leukocytosis, noting that these patients are prone to infections because the accumulated glycogen serves as a substrate for the development of pathogens (15).

![Figure 4. Growth of case 1 relative to the 3rd percentile of WHO standards](image1)

![Figure 5. Growth of case 2 in relation to the 3rd percentile of WHO standards.](image2)
It is argued that this is GSDIIIa because it highlights the elevation of AST and ALT, in contrast, invariant IIIc transferase activity is normal while in subtype IIId is poor (5). Another distinction is elevated levels of CK, which indicates muscle engagement, which is not observable in GSDIIIb (10).

Both patients were valued at CANIA, being graduated with a dietary plan characterized by high protein content, frequent meals with slow absorption carbohydrates such as cornstarch with restriction of carbohydrates impossible to be metabolized directly into glucose.

Currently, there are limitations due to the lack of access to genetic studies in Venezuela, this prevents the etiological diagnosis of pathology. Also, the mother of the patients reported that there are socioeconomic barriers that make it difficult to comply with the diet and perform some tests such as echocardiography, however, they have managed to adapt despite the obstacles involved.

Many cases of glycogenosis are probably not diagnosed correctly. Knowing these diseases allows to establish differential diagnosis or diagnostics in children with hepatomegaly, so it is intended to expand knowledge about GSDIII to facilitate early diagnosis, treatment, and decrease complications improving the prognosis of patients.

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