Hepatic glycogenosis as a cause of hepatomegaly in children and adolescents with type 1 diabetes mellitus

Glicogenose hepática: causa de hepatomegália em crianças e adolescentes com diabetes mellitus tipo 1

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SUMMARY

Secondary hepatic glycogenosis is an underrecognized complication of long-standing type 1 diabetes. It has been described as the first cause of hepatomegaly in children and adolescents with type 1 diabetes and poor metabolic control. It must be distinguished from other causes of hepatomegaly and elevated liver enzymes such as nonalcoholic fatty liver disease. The authors report the case of a fifteen-year-old male with type 1 diabetes for 4 years and not compliant to treatment who presented with hepatomegaly and elevated liver enzymes. Other possible causes were excluded. Liver biopsy confirmed periodic acid-Schiff-positive deposits of glycogen in cytoplasm and nuclei. During follow-up, a correlation between better metabolic control and reduction in liver size and enzyme levels has been shown. In most cases secondary glycogenosis is reversible with adequate glycemic control. The performance of liver biopsy remains a matter of controversy.

KEY-WORDS

Glycogenosis; Glycogen; Diabetes mellitus type 1; Hepatomegaly; Child.

RESUMO

A glicogenose hepática secundária é uma complicação subdiagnosticada da diabetes mellitus tipo 1 de longa duração. É descrita como primeira causa de hepatomegália em crianças e adolescentes com diabetes mellitus tipo 1 de longa duração e mau controlo metabólico. Deve ser diferenciada de outras causas de hepatomegália e elevação das enzimas hepáticas, como esteatose hepática não alcoólica. Os autores descrevem o caso de um rapaz de 15 anos com diabetes tipo 1 com 4 anos de evolução e má adesão à terapêutica, que surgiu com hepatomegália e elevação das enzimas hepáticas. Foram excluídas outras causas possíveis. A biópsia hepática confirmou a presença de depósitos citoplasmáticos e intranucleares de glicogénio positivos na coloração por PAS (*periodic acid-Schiff*). Verificou-se correlação entre períodos de melhor controlo metabólico e diminuição das dimensões hepáticas e dos níveis enzimáticos. A

glicogenose hepática secundária é reversível mediante controlo glicémico adequado. A indicação para realização de biópsia hepática não é consensual.

PALAVRAS-CHAVE

Glicogenose; Glicogénio; Diabetes mellitus tipo 1; Hepatomegália; Crianças.

ABBREVIATIONS

DM, diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HbA1c, glycosylated hemoglobin fraction; LDL, low-density lipoprotein; BMI, body mass index; MDI, multiple daily injections; NPH, neutral protamine Hagedorn; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; PAS, periodic acid-Schiff.

INTRODUCTION

Diabetes mellitus (DM) is a systemic disease which may cause several hepatic changes. Non-alcoholic fatty liver disease (NAFLD), which comprises steatosis and steatohepatitis (NASH), occurs mostly in type 2 diabetes and is associated with obesity and insulin resistance[1-5]. Secondary hepatic glycogenosis has been considered a rare condition; yet, it has been described as the first cause of hepatomegaly in children and adolescents with poorly controlled long-standing type 1 diabetes, although it can also occur in patients with type 2 diabetes[1-3,6,7]. The importance of distinguishing between NAFLD and secondary glycogenosis is that the former may progress to irreversible fibrosis and cirrhosis, whereas the latter has a better prognosis, being reversible upon optimization of glycemic control[1-7].

We report the case of a 15 year-old male with poorly controlled type 1 diabetes who presented with hepatomegaly and elevated transaminases.

CASE REPORT

A 15-year-old boy with type 1 DM presented at one of his regular visits at our hospital with hepatomegaly extending 3 cm below the right costal margin and elevated transaminases. Diabetes had been diagnosed at the age of eleven, but soon after the diagnosis he started to evidence poor glycemic control [glycosylated hemoglobin fraction (HbA1c) 8,2-11,0%] with frequent episodes of hyperglycemia. He often skipped insulin administrations and needed high doses of insulin due to excessive food intake. Three years after diagnosis, his blood tests revealed hyperlipidemia for the first time [total cholesterol 232 mg/dL, low-density lipoprotein (LDL)-cholesterol 104 mg/dL and triglycerides 443 mg/dL).

The patient referred no symptoms and had no history of alcohol or narcotic abuse or regular use of any other medication besides insulin. The family history was unremarkable. He appeared well nourished, his weight was 66 kg (75th percentile), the height was 169,5 cm (between 25th and 50th percentiles) and the body mass index (BMI) was 23,0 kg/m^2 (between 75th and 85th percentiles). He had a normal pubertal development. There were no other remarkable findings on physical examination.

By then, he was on multiple daily injections (MDI) treatment with premeal lispro insulin and neutral protamine Hagedorn (NPH) insulin before breakfast and before supper (insulin sensitivity factor 15 mg/dL, insulin-to-carbohydrate ratio 3 U/1 exchange) at a total dose of 1,4 U/kg/day.

On laboratory examination, complete blood count was normal and transaminases were elevated [aspartate transaminase (AST) 343 U/L, alanine transaminase (ALT) 384 U/L]; HbA1c was 10,8%. Abdominal ultrasound demonstrated enlarged liver with regular contour and homogenously reflective echostructure, suggesting moderate steatosis, and also homogenous splenomegaly.

Because of persistence of poor metabolic control (in spite of insulin treatment with 1,7 U/kg/day), hepatomegaly and further rise of transaminases (AST 1236 U/L, ALT 925 U/L), he was admitted in our Pediatric ward for investigation and optimization of glycemic control, with collaboration of the Gastroenterology Department. The following hypotheses were considered: non-alcoholic steatohepatitis (NASH), hepatitis (viral or autoimmune) and metabolic or infiltrative hepatic disease. Liver function tests except for transaminases and gamma-glutamyl transferase (GGT) were within reference range (Tables I and II). Viral serologies and autoimmunity antibodies were negative (Table II). Metabolic disorders such as hemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency were ruled out (Table II).

Subsequent diagnostic work-up included an abdominal ultrasound with Doppler that gave no additional information, and a percutaneous liver biopsy which showed moderate to severe homogenous macrovesicular steatosis (60-70%) without fibrosis and a large number of hepatocytes with periodic acid-Schiff (PAS)-positive intranuclear glycogen deposits (Figure 1). Hepatic copper was within normal range (9,0 µg/g of dry liver; reference range <50 µg/g). At this point hepatic glycogenosis secondary to poor glycemic control was the most likely diagnosis.

Under a tight control of food intake and supervised insulin treatment, there was a gradual improvement of glycemic values with lower insulin dose requirement and reduction of lipid and liver enzymes levels (Table I). Hepatomegaly decreased progressively until it was no longer detected on

TABLE I: Evolution of laboratory tests performed during first hospital admission, demonstrating reduction of the levels of liver enzymes and lipids.

	AST (U/L)	ALT (U/L)	GGT (U/L)	Chol (mg/dL)	TG (mg/dL)
Day 1	541	549	NP	NP	NP
Day 5	426	503	290	252	296
Day 9	175	291	235	178	152
Reference range	10 – 47	14 – 72	15 – 73	<201	35 – 160

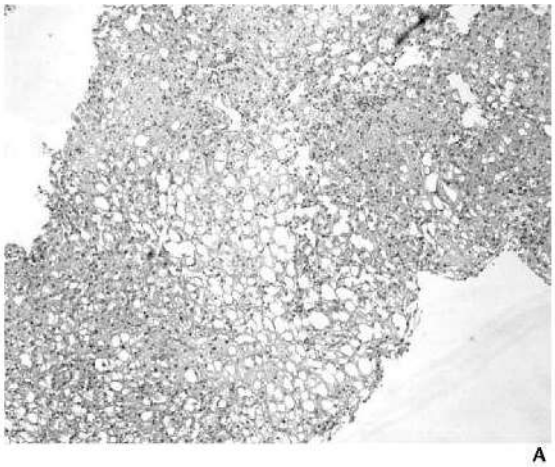
AST – aspartate transaminase; ALT – alanine transaminase; GGT – gamma-glutamyl transferase; Chol – total cholesterol; TG – triglycerides; NP – not performed.

TABLE II: Results of laboratory investigations.

	Results	Reference range
Liver tests		
ALP (U/L)	155	130 - 525
Total bilirubin (µmol/L)	11	0 - 24
Albumin (g/dL)	4,7	3,9 – 5,0
Prothrombin time (sec)	11,45	C = 13,35
Viral serologies		
HAV, HBV, HCV	Negative	
EBV, CMV, HSV 1 and 2	Negative for acute infection	
Autoimmunity tests		
ANA	Negative	
ASMA	Negative	
Anti-LKM antibody	Negative	
Anti-LC1 antibody	Negative	
SLA	Negative	
AMA	Negative	
Other tests		
Lactic acid (mmol/L)	2,3	0,7 – 2,1
Ammonia (µmol/L)	4	9 – 33
Alpha-1 AT (mg/dL)	99	93 – 220
Copper, serum (µg/dL)	143	70 – 140
Copper , urine (µg/L)	8,6	2,0 – 80,0
Ceruloplasmin (mg/dL)	50	22 – 58
Iron (µmol/L)	25,9	8,8 – 32,4
Ferritin (ng/mL)	242	20 – 250
TIBC (µmol/L)	66,9	46,8 – 82,7
Transferrin saturation (%)	38,7	20,0 – 50,0

ALP – alkaline phosphatase; C – control; HAV – hepatitis A virus; HBV – hepatitis B virus; HCV – hepatitis C virus; EBV – Epstein-Barr virus; CMV – cytomegalovirus; HSV – herpes simplex virus; ANA – antinuclear antibody; ASMA – anti-smooth muscle antibody; LKM – liver-kidney microsomal; LC1 – liver cytosol 1; SLA – soluble liver antigen; AMA – anti-mitochondrial antibody; Alpha-1 AT – alpha-1 antitrypsin; TIBC ¬– total iron binding capacity.

FIGURE 1: Liver histology. (A) Macrovesicular steatosis (hematoxylin and eosin). (B) Enlarged nuclei (arrows) with peripherally displaced material suggesting accumulation of substance inside (hematoxylin and eosin). (C) Abundant cytoplasmic and nuclear (arrows) glycogen deposits demonstrated by periodic acid-Schiff stain.



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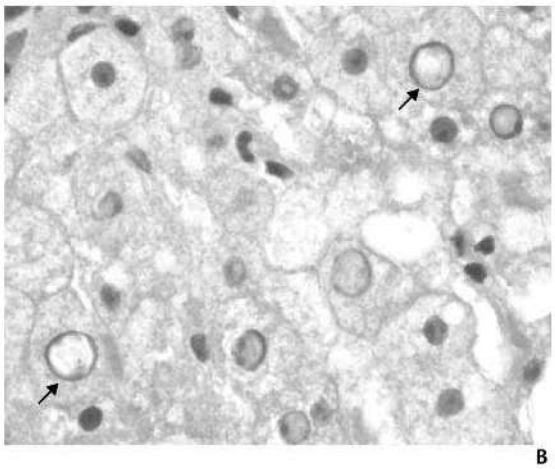

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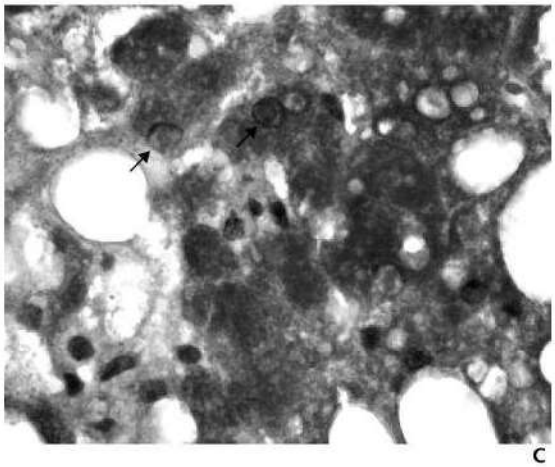

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physical examination on the 9th day after admission. He was discharged home on the 12th day after admission.

Since the diagnosis, the patient has had periods of reasonable metabolic control

TABLE III: Laboratory test results during follow-up in the period of best and worst metabolic control (respectively 12 and 18 months after onset of symptoms). There is correlation between lower HbA1c and lower levels of liver enzymes.

	Best control	Worst control
HbA1c (%)	8,8	10,2
AST (U/L)	133	929
ALT (U/L)	175	1384
GGT (U/L)	168	783

HbA1c – glycosylated hemoglobin fraction; AST – aspartate transaminase; ALT – alanine transaminase; GGT – gamma-glutamyl transferase.

interspersed with others of poor metabolic control, in spite of optimization of insulin treatment (insulin glargine as basal insulin and lispro as premeal insulin, instituted seven months after initial signs), which he is still not compliant to. Those periods of better glycemic control are accompanied by reduction in liver size and liver enzyme levels (Table III), although maintaining palpable hepatomegaly and hepatic steatosis pattern on abdominal ultrasound.

DISCUSSION

Secondary hepatic glycogenosis is characterized by accumulation of glycogen in the cytoplasm and nuclei of hepatocytes. It is associated with long-standing type 1 DM and poor metabolic control. Two possible mechanisms have been implicated: repeated episodes of hyperglycemia and administration of high doses of insulin[1,3,7,8].

Glucose enters the hepatocyte via passive diffusion, independent of insulin[1-5,8]. Once in the cell, it is converted into glucose-6-phosphate by glucokinase and is thereby trapped in the hepatocyte, increasing its intracellular concentration[4,5,9]. Subsequently, it is transformed into glycogen via glycogenesis[2,9]. Glycogen synthase, the rate-limiting enzyme in this process, is enhanced by excessive amount of insulin administered to cope with hyperglycemia, and also by high cytoplasmic glucose[4,5,7]. On the other hand, in case of insufficient insulin, as occurs in diabetic ketoacidosis, lipolysis is promoted,

which accounts for hyperlipidemia[1]. Ketone bodies stimulate synthesis of cortisol, which further enhances hyperglycemia and lipolysis[1]. The balance between glycogenesis and glycogenolysis, essential for determining a normal level of hepatic glycogen, is disturbed by frequent hypoglycemia and hyperglycemia often seen in poorly controlled diabetic patients[2,9].

Glycogen hepatopathy may manifest clinically by abdominal pain, early satiety, hepatomegaly and occasionally splenomegaly[1,3]. The short stature, delayed sexual development and cushingoid appearance which characterize Mauriac syndrome, not present in our patient, arise in response to elevated cortisol already described[1,4,5,9]. The intracellular accumulation of glycogen causes cell lesion and consequent rise of transaminase levels of variable range (50 – 1600 U/L)[1,9]. It is not usually accompanied by abnormalities in other liver function tests, such as albumin or prothrombin time[1,5]. All these changes are reversible after optimization of metabolic control, in a period varying from 2 to 14 weeks[2,4,5,9]. Although this was never achieved in our patient, we verified correlation between periods of improved control and reduction in liver size and levels of liver enzymes. Therefore, in face of the risk of hepatic glycogenosis and NAFLD, screening for liver enzymes, particularly transaminases, is recommended in a patient with type 1 DM with hepatomegaly, dyslipidemia or poor metabolic control.

The investigation of hepatomegaly and raised transaminases presenting in a type 1 diabetic child or adolescent should rule out diseases such as viral hepatitis, autoimmune or toxic hepatitis, hemochromatosis, Wilson's disease and other metabolic or infiltrative hepatic diseases[4]. Clinical data are usually enough for excluding primary glycogen storage disease[5,7].

The performance of liver biopsy remains a matter of controversy in the literature. Some authors defend its absolute need for distinction between hepatic glycogenosis and NAFLD, which is impossible on clinical grounds, and for information on prognosis[3]. Others prefer delaying this invasive procedure until diagnosis of secondary glycogenosis is supported by reversal of the clinical and laboratory findings upon attainment of a correct metabolic control[1,2,4,7]. Considering the lack of consensus about this issue and the fact that our patient never achieved a lasting euglycemic period, we decided to perform liver biopsy, which allowed definitive diagnosis by demonstrating accumulation of glycogen in cytoplasm and nuclei of hepatocytes. Characteristically, fibrosis and necrosis are absent or insignificant[1,5,9]. Concomitant steatosis has been reported in the literature in 10 to 50% cases[1,7,9]. In this case, given the presence of hyperlipidemia, coexistence of steatosis was not surprising, which might worsen prognosis.

In summary, this case report contributes to emphasizing the importance of secondary hepatic glycogenosis as a possible under recognized entity in children and adolescents with poorly controlled type 1 diabetes who present with hepatomegaly and raised transaminases. Unlike NAFLD and other hepatopathies, it has a good prognosis and is reversible after optimization of metabolic control.

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