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RESEARCH ARTICLE

HEPATIC GLYCOGENOSIS ASSOCIATED WITH TYPE 1 DIABETES (A CASE REPORT)

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Abstract

Background:insulin deficiency in diabetes leads to many complications. Hepatocyte glycogen overload, previously known as Mauriac syndrome, is one of them. It is a rare syndrome initially described in type 1 diabetic children in whom significant hyperglycemia is followed by administration of high doses of insulin.
Case Presentation: We present the case of a 17-year-old girl withuncontrolled type 1 diabetes. Admitted for growth retardation in addition to impuberism. The clinical examination revealed a weight delay associated with a distended abdomen and hepatomegaly. The laboratory work-up showed cytolysis and anicteric cholestasis with negative viral serologies and immunological assessment. Hepatic ultrasound revealed a 19 cm hepatomegaly without any focal signs or steatosis, as confirmed by a bili-MRI that proved the same finding. A management based on insulin therapy was introduced. The etiological investigation of the hepatic disturbances was negative.
Conclusions: The course was satisfactory under appropriate insulin therapy. The diagnosis of hepatic glycogenosis was based on a combination of anamnestic, clinical and histological findings, given the absence of other abnormalities responsible for the liver disturbances

Introduction:

Chronic insulin deficiency in diabetes can lead to a number of complications, including the hepatocyte glycogen overload, previously known as Mauriac syndrome, this complication is relatively rare and occurs in children with type 1 diabetesmellitus (T1DM) treated with high doses of rapid-acting insulin [1,2]. The clinical signs associated with this syndrome are dominated by "growth retardation, hepatomegaly and cushingoid signs"[1,2,3]. The use of long-acting basal insulins has resulted in better glycaemic control and a lower incidence of this complication[2,3].

We report here a case of Mauriac syndrome diagnosed in an adolescent girl with T1DM admitted to the department for investigation of delayed weight gain and impuberism.

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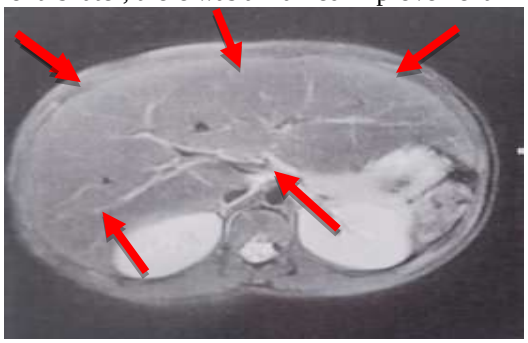
Case Presentation:
A 17-year-old female patient, diagnosed with type one diabetes since the age of four, badly followed up, with no history of acute complications such as ketoacidosis or severe hypoglycemia. She was initially admitted for the management of delayed puberty linked to glycemic uncontrol.

On admission, the patient was in good general condition with a body mass index of 17 .3 kg/m2(Weight: 38 kg (-2.2 standard deviation), Height: 1.485 m (-2.4 standard deviation)), Blood pressure at 101/82 mmHg, heart rate at 82 pulse/minute, capillary blood glucose at 2.61 g/l, and urine dipstick showing negative glycosuria and ketonuria. Abdominopelvic examination highlighted a distended abdomen, hepatomegaly at 19 cm, with no splenomegaly in an impubescent patient. The biological workup showed hepatic cytolysis (ASAT = 81 × normal (N)), ALAT = 31 × N), anicteric cholestasis (γGT = 39 × N, alkaline phosphatase = 1.6 × N, total bilirubinemia = 11mg/l), without any associated stigma of hepatocellular insufficiency (prothrombin level = 100%), HbA1c of 13.7%, along with a normal blood ionogram and renal function. Viral serologies (Epstein-Barr virus, Hepatitis A Virus,Hepatitis B Virus, Hepatitis C Virus, Hepatitis E Virus, Cytomegalovirus and Human Herpesviruse) were negative. The immunological workup (anti–liver-kidney microsomal antibody, anti-smooth muscle antibodies and antimitochondrial) was negative.

Radiological examinations in particular the Bili MRI objectified hepatomegaly of up to 19 cm with no other associated lesions (Fig. 1 & 2).

The patient underwent a liver biopsy, which histological study indicated an isolated hepatocyte ballooning without necrosis, inflammatory infiltrate, cholestasis or fibrosis. The diagnosis of hepatocyte glycogen overload (HG) was adopted, after which the patient had received dietary education and started basal bolus insulin therapy. A few months later, there was a marked improvement in blood sugar levels, as well as normalisation of hepatic cytolysis.



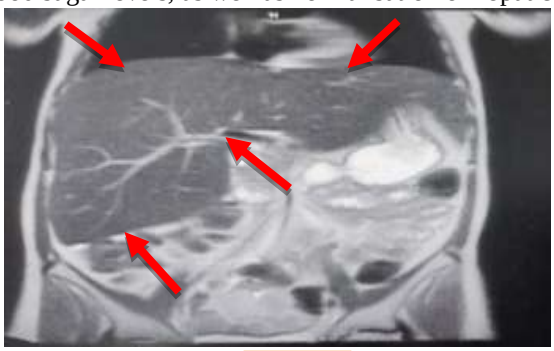


Figure 1: Cross section of Bili MRI showing homogeneous hepatomegaly.
Figure 2: Frontal section of Bili MRI showing a homogeneous hepatomegaly.

Discussion:

In 1930 Pierre Mauriac described this complication for the 1st time with a typical clinical presentation consisting of the triad hepatomegaly, growth delay and delayed puberty in type 1 diabetic children treated with high doses of fast-acting insulin [4,5].

This syndrome can present in 2 forms, one with obesity which is generally of the cushingoid type, induced by alternating episodes of hyperglycaemia treated massively with insulin and hypoglycaemia with a significant reduction in insulin doses[5]; Periods of overinsulinization seem to be essential for the development of obesity and the induction of hyperadrenalism[6].

The second form has been reported recently, in patients with no history of alternating hypoglycemia and ketoacidosis[7]. Like the case of our patient who had the notion of long-term imbalance without acute complication, this syndrome occurs mainly in patients treated with short-acting insulin[7],The pathophysiology of this syndrome remains imperfectly understood. The combination of episodes of hyperglycaemia and treatment with high doses of insulin can lead to excessive glycogen storage in the liver through strong activation of glucokinase and glycogen

synthetase, trapping glucose 6 phosphatase and transforming it into glycogen, leading to the development of hepatomegaly[2,8].

Growth retardation and delayed puberty may be secondary to chronic tissue deficiency of insulin and insulin growth factors, but the precise pathophysiology of these associated complications is not yet clear[2,6]. This is in line with the presentation of our case, in which the etiological investigation of the statural delay and impuberism was negative.

There is a hypothesis involving a mutation in the genes that regulate the activity of the enzymes glycogen synthase and glucose 6-phosphatase, making them hyperactive, but this remains an unsubstantiated argument to explain the hepatic storage of glycogen in HG in cases of diabetes mellitus[5,9].

Michael J. MacDonald & al. have provided a possible answer to the reasons for this pathology by demonstrating, in a patient suffering from Mauriac syndrome, the existence of a mutation of the hepatic glycogen phosphorylase kinase, of which the physiological role is to activate glycogen phosphorylase, itself allowing the degradation of glycogen [10]. The authors show that this mutation is dominant and that it totally inhibits glycogenolysis, which explains the accumulation of hepatic glycogen[10].

It is also known that the enzyme involved here (hepatic glycogen phosphorylase kinase) is physiologically strongly inhibited by glucose [11]. Therefore, it is understandable that in case of diabetic disequilibrium, this enzyme may be doubly inhibited, by high blood glucose and by the mutation[11]. These results are rarely observed today because of the widespread use of long-acting insulin. Fluctuating episodes of hyper and hypoglycaemia may be accompanied by activation of counter-regulatory hormones, particularly cortisol, leading to a state of hypercorticism and clinical signs of cushingoidism[2,12]. These signs are present in children and adolescents during puberty[2,3,4].

In terms of imaging, the abdominal ultrasound performed on our patient showed hepatomegaly and an appearance of overload reflecting chronic glycogen storage. Additional magnetic resonance imaging seemed necessary as it is more sensitive in differentiating steatosis from hepatic glycogenosis [13]. Before diagnosing hepatic glycogenosis, it is essential to rule out other causes of hepatomegaly, in particular viral, metabolic, autoimmune and obstructive diseases[2,9].All of which are ruled out inour case.

For diagnosis, it showed isolated hepatocyte ballooning. It may reveal abnormal giant mitochondria. These findings point to a defect in the mitochondrial respiratory chain [14,15]. Nevertheless, some authors do not recommend a biopsy if the liver workup is returned to normal with good glycemic control [16].

A higher dose of insulin appears to be necessary for good glycaemic control in patients with hepatic glycogenosis (1.33 versus 0.6 to 1.1 IU/kg)[1,2].

Maintaining good glycaemic control means that the disease progresses well and liver damage disappears within a few weeks[2,17].

Conclusion:-

even though Mauriac syndrome is a rare complication of diabetes it should not bedisregarded as differential diagnosis in diabetic patients with hepatomegaly. The diagnosis is based on a number of clinical arguments, but the definitive diagnosis is histological and the treatment is based on the control of diabetes.

Compared to other liver diseases associated with diabetesHG is a favourable diagnosis because of its benign nature and good prognosis.

List of Abbreviations:

T1DM: type 1 diabetes mellitus
HG: hepatocyte glycogen overload

Declarations:

-Ethics approval:

Informed consent has been obtained from the patient.

-Consent for publication:
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

-Availability of supporting data:
The dataset of the current study is available from the corresponding author upon: Samira Handa (samira.handa@usmba.ac.ma)

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-Authors' contributions:
Samira Handa ,Mohamed Amine Essafiand Khawla Salhi wrote and revised the main manuscript. Samira Handa took the photos and prepared them. Samira Handa and Khawla Salhi checked the references. Hayat Aynaou and Houda Salhi reviewed the entire manuscript. All authors read and approved the final manuscript.

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