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RESEARCH ARTICLE

HEPATIC GLYCOGENOSIS: AN UNDER-RECOGNIZED COMPLICATION OF POORLY CONTROLLED DIABETES MELLITUS TYPE 1(THREE CLINICAL CASES)

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Abstract

Hepaticglycogenosis is an inherited abnormality characterized by excessive glycogen accumulation in hepatocytes. It is a hepatic complication of poorly controlled type 1 diabetes mellitus. It combines hepatomegaly, growth failure, and hepatic cytolysis as well ascushing-like feature. Hepatic glycogenosis is only diagnosed by liver biopsy.

We report the observation of three clinical cases:

N°1: A 16-year-old male, with type 1 diabetes mellitus since a year. Admitted for keto-acidosic decompensation, he presented dyspnea, a distended abdomen with painless hepatomegaly. Abdominal ultrasound showed 21 cm homogeneous hepatomegaly. The anatomo-pathological study of the liver biopsy confirmed the diagnosis of hepatic glycogenosis.N°2:An 18-year-old female, with type 1 diabetes mellitusfor 14 years with a severe growth failure, she presented a major cytolysis with hepatic cholestasis for 5 years. Abdominal ultrasound showed homogeneous hepatomegaly.Theanatomo-pathological study of the liver biopsy confirmed the diagnosis of hepatic glycogenosis.N°3:A 19-year-old female, with type 1 diabetes mellitusfor 8 years, epilepsy and delayed puberty. The biological check-up had objectified a very significant cytolysis and major dyslipidemia. Abdominal ultrasound shows hepatomegaly associated with hepatic steatosis. A liver biopsy was indicated, but not performed as the patient was lost to follow-up.The discovery of hepatomegaly in a patient with poorly controlled type 1 diabetes mellitus must evoke a variety of diagnoses. Although hepatic glycogenosis is a rare diagnosis, it should not be ignored by the clinician.Through these clinical cases, the pathophysiology of hepatic glycogenosis, complications as well as therapeutic management has been discussed.

Introduction:-

Mauriac's syndrome or hepaticglycogenosisis a hereditaryanomalythatischaracterizedby an overload of glycogen hepatocytes rarely observed in young people with poorly controlled type 1 diabetes mellitus (T1DM). This imbalance leads to many complications, which includes Mauriac's syndrome. It is a rare syndrome observed in children with type 1 diabetes where episodes of significant hyperglycemia ensue followed by the administration of

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high doses of insulin [1]. It clinically includes growth failure, hepatomegaly and hepatic cytolysis as well as cushing-likefeature [1,2]. The incidence of this syndrome decreased significantly with the introduction of long-acting insulin resulting in better blood glucose control [2]. This complication is exceptionally observed in adults.

CASEREPORTS:

We're presenting three clinical cases:

Clinical case N °1: This is a 16-year-old patient, with T1DM since a year treated by basal-bolus insulin plan, with the notion of repeated hospitalizations for episodes of Diabetic keto-acidosis (DKA). He was admitted for keto-acidotic decompensation, clinically we found dyspnea, a distended abdomen with painless and homogeneous hepatomegaly, a BMI at 15 kg/m², capillary blood glucose at 5g/l with 3 crosses of glucose and acetone on the urine test strip. In addition, his clinical growth was normal. Intravenous insulin therapy and hydro electrolyte intake were administered. At the same time, an etiological investigation was initiated. Renal and liver function assessments were normal, with on abdominal ultrasound a homogeneous hepatomegaly of 21 cm of regular contours of homogeneous echo structure without detectable nodular lesions, the serologies of viral hepatitis were negative. Autoimmune liver disease, overload diseases as well as celiac disease have been eliminated. Abdominal commuted tomography (CT) confirmed this homogeneous hyperdense hepatomegaly suggesting hemochromatosis or glycogen storage disease (Fig 1). Hemochromatosis was eliminated by serum iron assays, ferritinemia and transferrin saturation coefficient which were normal. The ophthalmological examination had noted the absence of the Kayser-Fleischer ring. The anatomopathological study of the liver biopsy affirmed the diagnosis of by showinghepatocellular glycogen accumulation(Fig 2: A, B, C).

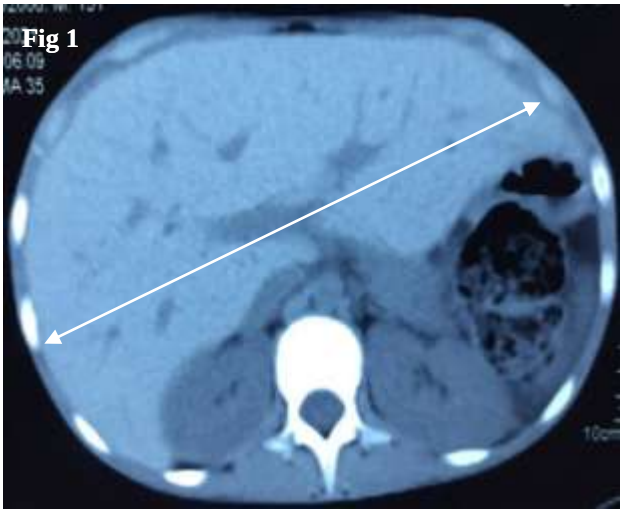
Fig 1

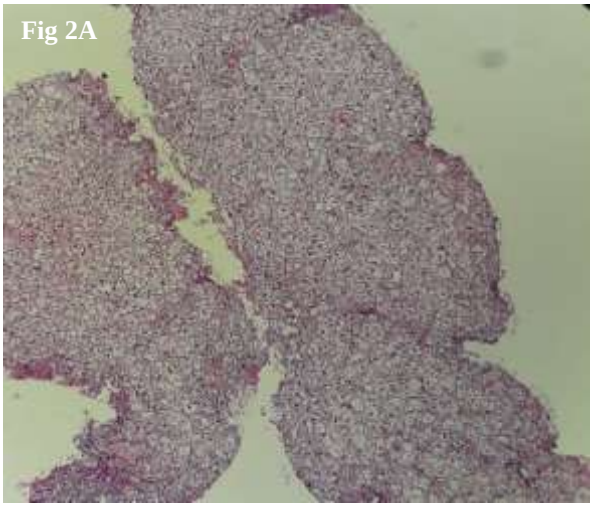
Fig 2A

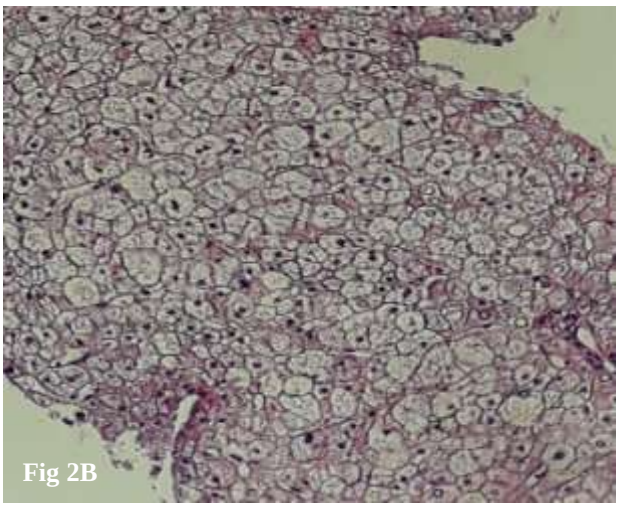
Fig 2B

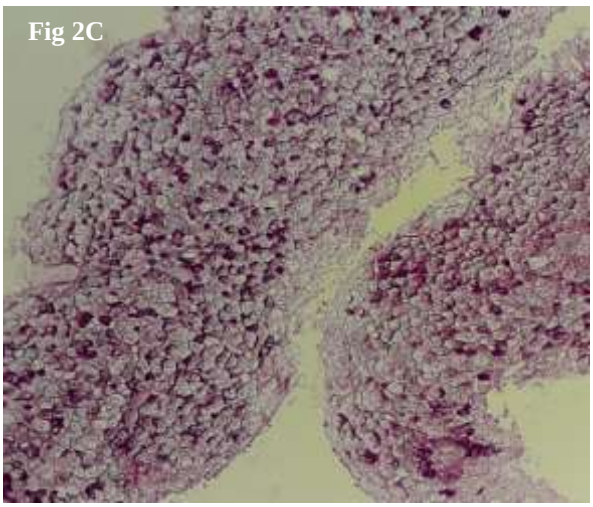
Fig 2C

Figure 1: Axial commuted tomography scan, cross-sectional view showing a hepatomegaly.
Figure 2A: Histological section of the liver showing hepatic parenchyma made up of large ballooning hepatocytes with abundant clarified cytoplasm (hematoxylin-eosin staining, low magnification).
Figure 2B: Histological section of the liver showing hepatic parenchyma made up of large, ballooning hepatocytes with abundant clarified cytoplasm (hematoxylin-eosin staining, medium magnification).
Figure 2C: Histological section of the liver with Periodic Acid Schiff (PAS) staining confirms the Hepatocellular Glycogen Accumulation.

Clinical case N°2: This is an 18-year-old patientwith T1DM since 14 yearspoorlycontrolledand a severegrowthfailure, with a weight of 29 kg (<-3 DS), a height of 127 cm (<-3 DS) and a BMI of 17 kg/m2, who had a major cytolysis for 05 years. The genitalexaminationhad found a stage of Tanner S1P1, without a malformativesyndrome pointing to Turner syndrome. The biological assessment had shown major cytolysis at 40 times the upper limit of normal. The abdominopelvic ultrasound had objectified a homogeneous hepatomegaly without dilation of the intra- and extra-hepatic bile ducts, withinternalgenitalorgans in place and of small size. Viral hepatitis serologies were negative, autoimmune liver disease and overload diseases as well as celiac disease were eliminated. The anatomopathological study of the liver biopsy puncture had confirmed the diagnosis of hepatic glycogenosis. In addition, all obvious causes of the growth delay have been eliminated.

Clinical case N° 3: This is a 19-year-old patientwith T1DM since8 yearspoorlycontrolledtreatedwith basal-bolus insulin plan, epilepsy and pubertal delay. The clinical examination during his 2nd episode of diabetic keto-acidosis (DKA) had objectified a normal weight and height for his age, a cushingoid appearance, abdominal distension in relation to a hepatomegaly with a smooth-edged confirmed by an ultrasound. The latter had shown the presence of fatty liver disease. The biological assessment revealed cytolysis at 5times the upper limit of normal, cholestasis and major mixed dyslipidemia. Viral hepatitis, autoimmune liver disease and overload diseases have been eliminated. A liver biopsy was indicated, but not performed as the patient was lost to follow-up. In this patient, in addition to optimized insulin therapy, we opted for an additional treatment based on Metformin, Ursodeoxycholic Acid and statin. Despite this association and also in the absence of a good adherence to the treatment, the balance of his diabetes was never achieved. The diagnosis of hepatic glycogenosis was retained by elimination of other etiologies.

The evolution was favorable in the first two cases after equilibration of diabetes through an optimization of insulin therapy with a clinicoradiological regression of hepatomegaly.

Through these clinical cases, we will discuss the pathophysiology of hepatic glycogenosis, complications as well as therapeutic management.

Discussion:-

Through the first two cases,wedescribe a hepaticglycogenosishistologicallyprovedwith a differentclinicalpresentation. The clinical feature of the 1st case is incomplete including an unbalanced type 1 diabetes (Fig 3)

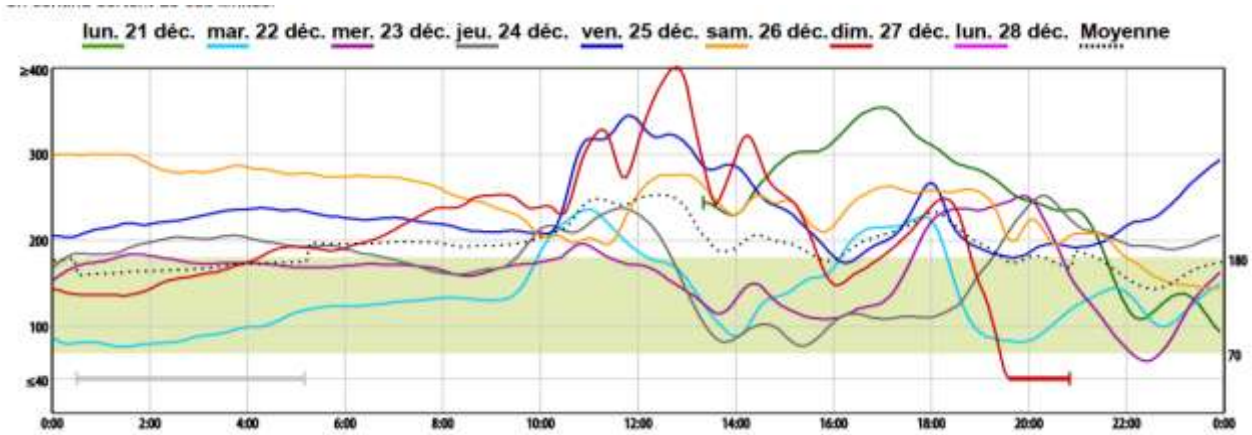

Figure 3:- Continuous recording of blood glucose showing the significant glycaemic excursions of the 1st patient.

recently diagnosed associated with hepatomegaly, on the other hand that of the 2nd case is more or less complete made of a very old unbalanced T1D, hepatomegaly, hepaticcytolysisand a stature-weight delay. As for the 3rd observation where there is a poorly controlled T1DM (Fig 4) with significant cytolysis and major dyslipidemia at the time of imbalance and delayed puberty, there is no histological diagnosis. In addition, cushingoid signs were present only in the last patient, and this can be explained by the duration of the evolution of diabetes.

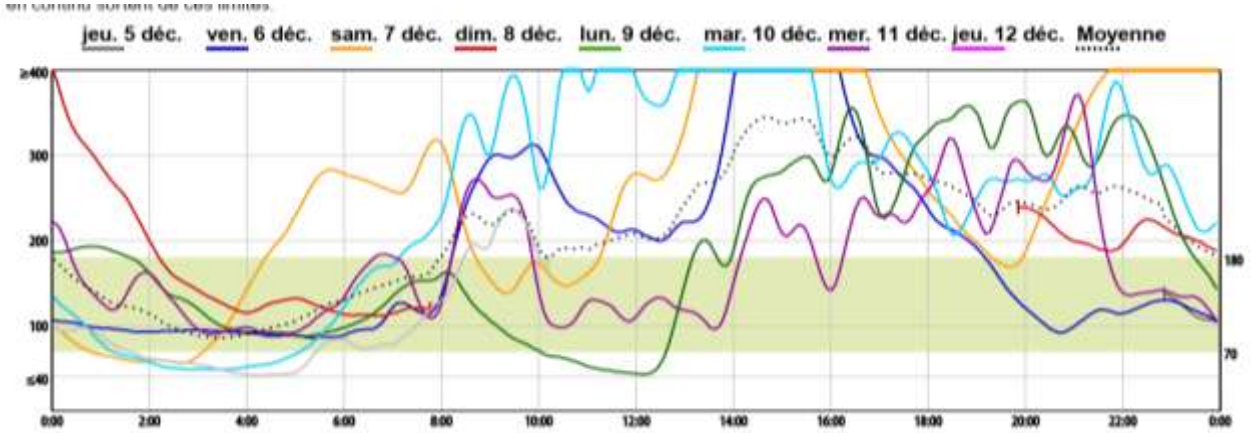

FIgure 4:- Continuous recording of blood glucose showing the significant glycaemic excursions of the 3rd patient.

Mauriac syndrome was first described by Mauriac in 1930 in children with T1D with growth delay, hepatomegaly andabdominal distension [1]. This name has been replaced by the term hepatic glycogenosis orhepatocellular glycogen accumulation [3].

Hepatic Glycogen storage disease results from total or partial disabilityof the liver to use the glycogen stored in it. There are several types (type I, III, V, VI, IX) of which type I is the most common (25% of cases, 1/100000 births). There are 2 subtypes of glycogenosis type I: type Ia related to glucose-6-phosphatase deficiency and type Ib related to glucose-6-phosphate transporter deficiency (G6P translocase). It affects the last stage of glycogenolysis and neoglucogenesis (Fig 5).

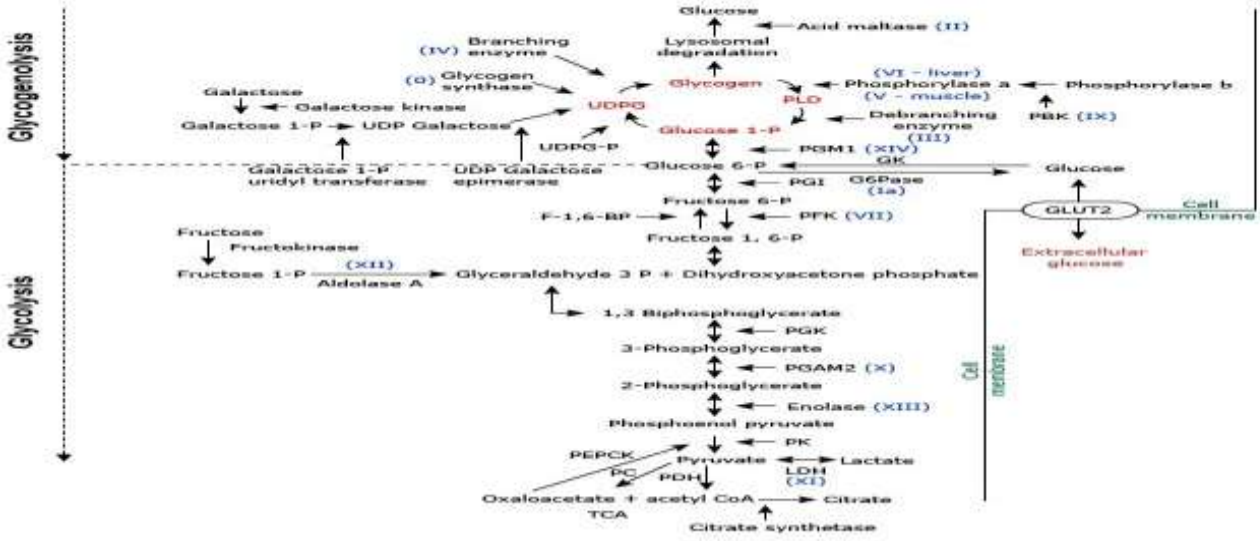

Figure 5:- Glycogen metabolism.

PFK: phosphofructokinase; PGM: phosphoglucomutase; PGK: phosphoglycerate kinase; PGAM: phosphoglycerate mutase; LDH: lactate dehydrogenase.

The pathophysiology of hepatic glycogenosis in patients with type 1 diabetes is imperfectly known. It appears to be linked to combined excess insulin and episodes of hyperglycemia. The mechanisms that contribute to hepatic glycogenosis in case of overconsumption of insulin associated with phases of hyperglycemia consist in excessive storage of circulating glucose in the form of intrahepatic glycogen by hyperstimulation of glycogenesis and inhibition of glycogenolysis (Fig 5); insulin activates glucokinase and glycogen-synthetase and inhibits glucose-6-phosphatase [3].

The pathogenesis of growth and pubertal delay is unclear but rather appears to be multifactorial: insufficient glucose in tissues, lack of insulin as a growth factor andhypercorticism may contribute to this.

Cushingoid signs present during glycogenosis are classically described in children [1,2]. Indeed, during the development period, large-scale documented fluctuations between hyperglycemia and hypoglycemia are accompanied by activation of counter-regulatory hormones with hypercorticism reactional to excess insulin [1,2]. Secondary hypercortisolism therefore seems to be responsible for the development of cushingoid obesity. This occurs mainly in children/adolescents, but is almost absent in those who have passed the pubertal period.

Hepatomegaly is secondary to the accumulation of glycogen in the liver. In case of major hyperglycemia, glucose passively enters hepatocytes via GLUT 2 (insulin-independent glucose transporter) and is rapidly transformed into glucose-6-Phosphate by glucokinase; significant insulin administration results in the transformation of glucose-6P into glycogen by glycogen-synthetase [4]. This phenomenon is amplified in case of repeated diabetic keto-acidosis (DKA) imposing high doses of insulin [2], as in our patients.

The diagnosis of certainty is histological based on the pathological study of the liver biopsy. In general, hepatic glycogenosis is characterized by several histological signs. After a conventional tissue preparation (fixation by formaldehyde solution and staining with hematoxylin and eosin), glycogen is usually removed from hepatocytes. Thus, the hepatocytes are diffusely inflated with a pale cytoplasm and an accentuation of the cell membranes, with displacement of the nuclei towards the cell periphery, the accumulation of glycogen in the hepatocytes is demonstrated by a periodic shift acid staining(PAS) (Fig 2C) [5].

Complications observed in children and adults often involve patients who have not received optimal management in the pediatric period or late diagnosis. The two main complications are hepatic and renal. On the hepatic level, there is a risk of development of hepatic adenomas after the age of 20 years, as well as their complications (hemorrhages and progression to adenocarcinoma) [6]. Close hepatic monitoring is therefore recommended by annual magneticresonanceimaging (MRI) in adults, an increase in size and structural changes are suspected and should be discussed surgical excision. The sensitivity of alpha-fetoprotein does not appear to be good in this population, although recommended [7]. On the renal side, in a published series of 288 patients, 13% was proteinuria and 31% microalbuminuria. It can be accompanied by hypertension and progress in the absence of appropriate management to end-stage renal failure [5]. It is usually a glomerulopathy whose pathophysiology is close to that of diabetic nephropathy.

These complications are prevented by a good metabolic balance without hypoglycemia ordiabetic keto-acidosis (DKA). Current data on adult populations are based on a study published in 2002, involving 288 patients with glycogenosis type Ia and Ib [8]. It is hoped that children who are will treated in infantile period will have fewer complications in adulthood, but it is not excluded that the ageing of the population may also lead to new and little-known complications.

The goal of treatment is to achieve glycemic control through optimal insulin therapy by avoiding hypoglycemia. A European consensus recommends maintaining blood sugar levels>0.65-0.70g/L, ensuring a good nutritional balance and preventing complications. In addition to maintaining euglycemia, the diet corrects secondary metabolic abnormalities, hyperlacticaemia, hyperlipidemia and hyperuricemia that are increased by fructose and galactose intakes. Thus, the management is based on the eviction of sucrose, fructose and lactose contained in sweet products, fruits and dairy products. Meals should consist mainly of starchy foods, protein sources (meat, eggs, fish) and vegetables (+/- fruits and dairy products authorized in limited quantities by some teams). The course is most often favorable thanks to the glycemic balance and the liver damage usually disappears in two to four weeks. However, the daily insulin doses required to achieve glycemic balance are often higher than in T1D subjects without hepatic glycogenosis (1.33 versus 0.6 to 1.1 IU/kg) [8,9].

Conclusion:-

The discovery of hepatomegaly in a type 1 diabetic patient should evoke a wide range of diagnoses. Although hepatic glycogenosis is a rare diagnosis, it should not be ignored by the practitioner especially in case of unbalanced diabetes associated with hepatomegaly and growth delay. The diagnosis of certainty is histological and the treatment is based on a good glucose control by optimized insulin therapy and a specific diet.

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