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Mauriac Syndrome with Reversible Clinical and Laboratory Findings After Glycemic Control (Case Series)

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Abstract
Mauriac syndrome is one of the rare complications of type I diabetes mellitus (DMI). It is characterized by marked hepatomegaly, growth, puberty delay, and the presence of markedly elevated transaminases and serum lipids. It has become even less common in the post-insulin era, but it still exists especially in patients with poor insulin compliance. It is important to recognize the disease as it has the potential for resolution following glycemic control. We report three adult cases presented with enlarged liver and elevated liver enzymes with poorly controlled type I diabetes mellitus. A Liver biopsy was performed in all patients and revealed hepatic glycogen infiltration. All of them showed improved clinical and laboratory findings after tight glycemic control by insulin therapy. We conclude that Mauriac's syndrome must be considered in any patient with DMI associated with hepatomegaly.

Keywords
Mauriac syndrome, diabetes mellitus, hepatomegaly, short stature, delayed puberty.

Introduction
Mauriac syndrome is one of the rare complications of diabetes mellitus type 1 (DM1), characterized by hepatomegaly (hepatic glycogenosis), delayed puberty, dyslipidemia, and elevated liver transaminase enzymes. We report three cases of Mauriac syndrome that showed reversible clinical and laboratory findings after tight glycemic control with basal-bolus insulin therapy plus a metformin regimen.

Case 1
A 14-year-old male presented to our clinic with significant hepatomegaly, short stature, and poor glycemic control. At the time of the first examination, he had a height of 127.5 cm, a weight of 25 Kg, and a body mass index (BMI) of 15.4 kg/m^2 which is less than the 3rd percentile expected for his age and sex regarding height and weight, with an absence of secondary sexual characters, indicating tanner stage 1. On physical examination, he had liver enlargement 4 cm below the subcostal margin, but without jaundice, enlarged spleen, edema, or ascites. While looking for a cause of his short stature and hepatomegaly, the following laboratory investigations were done showing the following results: blood sugar level of (238 mg/dL), glycated haemoglobin (HbA1c) of (14 mg/dl), a total cholesterol level was (271 mg/dL), serum triglycerides of (175 mg/dL), the thyroid functions were normal, coeliac disease serology was negative, and insulin-like growth factor 1 (IGF-1) level was normal. According to the Greulich-Pyle atlas for bone age, the patient was estimated as 10 years old, his growth hormone (GH) peak level was below normal after the growth hormone stimulation test, and liver enzymes showed 10 times increase than normal levels, but his alkaline phosphatase was normal, as well as his total bilirubin and prothrombin time were also within normal range. To exclude other causes of hepatomegaly we ordered antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA),anti-smooth muscle antibodies (ASMA), also anti-neutrophil cytoplasmic antibodies (ANCA), all of them came back negative, excluding autoimmune hepatitis, serology tests for, cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis viruses A, B & C markers, human immunodeficiency virus(HIV) were all negative as well which excluded recent infections as a cause of the liver enlargement, to exclude minerals deposits we also ordered an iron panel, copper and ceruloplasmin levels which all came back with normal values. Abdominal ultrasound confirmed the presence of marked hepatomegaly with bright echogenicity. This leads us to consider more invasive tests, and a liver biopsy was performed, lobular architecture was preserved, but multiple swollen glycogen-laden hepatocytes were present, as well as nuclear glycogen pseudo-inclusions were present in the peri-portal area, and focal macrovesicular steatosis. Staining for iron and copper deposits was negative, and no evidence of inflammation or fibrosis was detected. So, a diagnosis of hepatic glycogenesis was confirmed. The management plan required tight metabolic control, so the patient was started on insulin Aspart premeal and insulin degludec as a basal dose, his mother received a diabetes education program. The patient was discharged on a basal-bolus regimen, metformin 500 mg, antioxidants, and omega-3 1000 mg/day. 2 Months later, laboratory tests showed a total cholesterol level of (195mg/dL), triglycerides level of (160 mg/dL), Alanine transaminase (ALT) (55 UI/L), aspartate transferase (AST) (69UI/L). Abdominal ultrasound showed shrinkage of liver size with clinical improvement in his overall performance.

Figure 1: patient with short Status.

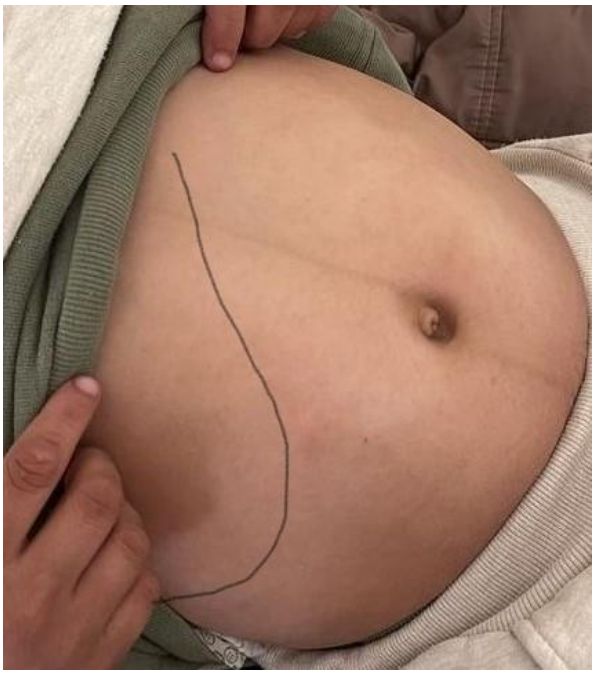

Figure 2: Enlarged Abdomen due to hepatomegaly.

Case 2

Male, 17 years old, with type I diabetes mellitus (DM1) complicated with severe retinopathy. His BMI was (34 kg/m^2), he had poor glycemic control since childhood, ongoing home treatment with premixed insulin twice per day, he presented with HbA1c (14.5%), and a history of recurrent diabetic ketoacidosis (DKA). 3 years ago, he started developing hepatomegaly and elevation of liver transaminases and triglycerides, his liver biopsy showed macro-vacuolar steatosis and mild fibrosis. After that, the patient was presented to the gastroenterology clinic for huge hepatomegaly. The laboratory investigations revealed persistent elevation of liver enzymes and triglycerides. His bilirubin levels, iron panel, and coagulation parameters were normal, and viral serologies and autoimmune studies were also negative. Abdominal MRI (magnetic resonance imaging) showed hepatomegaly with massive fatty infiltration. Repeated liver biopsy showed marked nuclear glycogenation, mild steatosis, and no fibrosis. We started a basal-bolus regimen along with metformin, fenofibrate, and antioxidants. Six months later, laboratory tests revealed a decline in his HbA1c (8.5%), liver enzymes were back to normal, and improvement in his lipid profile, as well as a reduction in his BMI to (30.2 kg/m^2).

Case 3

This 15-year-old male adolescent presented to our clinic complaining of short stature and delayed puberty. He was diagnosed with DM1 10 years ago and was on subcutaneous premixed insulin until the time of presentation but with poorly controlled blood sugar. This resulted in repeated hospital admission with DKA. Upon physical examination, the patient had short stature (138 cm); which is less than the 3rd percentile for his age, his weight in comparison to age was also less than the 3rd percentile, his BMI was (18 kg/m^2) which is between the 5th - 10th percentiles. He also had a bulged abdomen with hepatomegaly, delayed puberty, and muscle wasting. Further investigations showed ketonuria (++) and glycosuria, as well as elevated liver enzymes. Abdominal ultrasound revealed fatty infiltration of the liver, hepatomegaly, and altered liver echotexture. His fasting blood sugar was (420 mg/dL), HbA1c was 13.1% (normal < 6%), and microalbuminuria was more than 160 µg/mL (normal < 18 µg/mL), with increased albumin/creatinine ratio. The patient on the nerve conduction velocity test shows motor axonal neuropathy, microaneurysm on fundus examination, and osteopenia on the DEXA (dual-energy X-ray absorptiometry) scan. To confirm our diagnosis a liver biopsy has proven fatty infiltration with glycogen deposits. The patient was under diet control supervised by the dietitian and started on basal-bolus insulin, metformin 500 mg, calcium, and vitamin D3. 2 months later, the patient's symptoms improved, and fasting blood sugar decreased up to (100 - 150 mg/dL) and there was an evident reduction in his hepatomegaly and his liver functions were back to normal. The patient was shifted to strict dietary management, and started on basal-bolus insulin, metformin 500 mg, calcium, and vitamin D3. 2 months later, the patient improved symptomatically, fasting blood sugar came down to (100 - 150 mg/dL) and there was a noticeable reduction in his hepatomegaly and his liver functions were back to normal.

Discussion

Pierre Mauriac first described this syndrome in 1930 [1], it is characterized by short stature, delayed puberty, dyslipidemia, cushingoid features, hepatomegaly, and increase transaminases in children with poorly controlled diabetes. Even though the mechanism of this disease remains poorly understood, some of the hypotheses described, include the elevation of insulin-like growth factor-binding protein-1 (IGFBP-1) due to hypoinsulinemia, which in turn result in suppression of Insulin-like growth factor (IGF) and cause growth failure [2]. Michael J et al., discovered for the first time in *2016 a* catalytic subunit mutation of glycogen phosphorylase kinase in the liver in 30 months child presented with type I diabetes, and the islet of Langerhans cell antibody–positive with hepatomegaly due to Mauriac syndrome [3].

Glycogenolysis enzyme Mutations cause hepatomegaly, growth failure, and the liver's unable to rapidly release glucose into the blood which is necessary to maintain a normal glucose level in the blood leading to hypoglycemia [4,5]. In diabetes high blood sugar alone can infrequently cause *deposition of* the glycogen in the liver (glycogen hepatopathy), but it does not reason of growth retardation, and massive deposition of glycogen in the liver as seen in Mauriac syndrome [6,7].

In addition, the mutation of the enzymes responsible for glycogen breakdown was also hypothesized, this idea originated from the typical finding of this disease which is glycogen deposits in liver biopsies [8], mostly seen in children, in these case studies we show that it can be present in adults as well. First, we need to exclude other causes of hepatomegaly, especially nonalcoholic fatty liver diseases [9], and the best way available now is liver biopsy which is still compulsory for the diagnosis of liver diseases [10,11]. Some studies have shown the presence of megamitochondria under the electron microscope, but this is not a consistent finding and therefore not considered a reliable diagnostic feature now [12].

We need to be cautious while managing these patients, as insulin can aggravate retinopathy if introduced rapidly, a stepwise approach with continuous insulin has shown promising outcomes, by avoiding massive swinging of glucose levels, which might direct us to consider insulin pump therapy in such patients, as it has already shown a favorable outcome in children with type I DM [13]. After therapy was initiated, improvement of liver enlargement and enzymes was noticed early, with variation in the time needed to achieve desired growth levels, due to factors like age and initial GH levels [14]. Insulin therapy and continuous monitoring of blood glucose is an appropriate approach to treat these patients and avoid complications.[15].

Conclusion

Despite the discovery of insulin and advances in the management of metabolic diseases, Mauriac syndrome cases are still seen, especially in developing countries. Early detection and management are important in stopping its progression, suspicion should be raised when the patient presents with type I DM, short stature, and hepatomegaly, which may warrant a liver biopsy as it is still the best test to confirm this diagnosis, improved clinical outcomes and lab findings were shown in management with basal-bolus insulin and metformin.

Author contribution

Dr. Negm composed the manuscript and literature review. Dr. Ahmed and Dr. Sherreen Elhariri had the analysis or interpretation of data for the work.

Ethical approval

Consent was obtained from all the patients.

Conflict of interest

Nil

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