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Original Research

The barriers of diagnosis: A clinical case of Mauriac syndrome

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Abstract

Mauriac syndrome is typically diagnosed in young patients with poorly controlled type 1 diabetes mellitus and is characterized by growth retardation, delayed puberty, cushingoid features, hypercholesterolemia, and hepatomegaly. However, the sole presenting feature of Mauriac Syndrome can be hepatic glycogenosis (glycogen accumulation in hepatocytes) in both adults and children. This case reports an 18-year-old patient with possible Mauriac syndrome. It was very difficult to confirm Mauriac syndrome, due to lack of compliance and acknowledgment of his medical condition. Differential diagnosis is made with non-alcoholic fatty liver disease and with non-alcoholic steatohepatitis. These two, in time, can progress to cirrhosis and later to hepatocellular carcinoma, whereas Mauriac syndrome is potentially reversible with optimal diabetes control.

Keywords: Mauriac syndrome, hepatic glycogenosis, type 1 diabetes mellitus, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis.

Background and aims

Mauriac syndrome is a rare entity, recognized as a complication of poorly controlled type 1 diabetes, which occurs mainly in children and adolescents and rarely in young adults. Besides type 1 diabetes, it associates short stature, growth deficit, dyslipidemia, cushingoid appearance, protuberant abdomen, hepatomegaly with transaminase elevation [1]. Although its incidence is not known, it has become even less common after the emergence of advanced insulin treatments but still exists [2].

It was described for the first time by Pierre Mauriac in 1930 in a girl, 10 years of age, with type 1 diabetes [1]. Since this first report several cases have been presented in the literature, with an increasing frequency of the reports in the past decade, probably not due to an increasing frequency of the syndrome but to increase awareness of its existence despite the access to modern insulin and insulin delivery systems. We have performed in PubMed a review of the literature published on the Mauriac syndrome in the past 20 years (from 1st of January 2001 until 31st of December 2021) and we identified 49 case presentations, studies, and reviews published, of which 41 in the past decade. Nowadays, most cases of Mauriac syndrome do not have all characteristics initially described and frequently the unique feature at presentation is the glycogenic hepatopathy [3, 4].

Here we present a case of a young adult with all characteristics of Mauriac syndrome with onset in pre-pubertal stage and persistence until adulthood despite access to insulin therapy and therapeutic education.

Case presentation

An 18-year-old male, belonging to low socioeconomic strata, was first admitted to Diabetes Center, Emergency Clinical County Hospital Cluj, on the 11th of August 2021 for poor glyco-metabolic control and extreme glycemic variability, with repeated episodes of hypoglycemia. The finger-prick test couldn't measure glycaemia at presentation, so the suspicion of diabetic ketoacidosis (DKA) was raised and later confirmed. Upon presentation, his vital signs were within normal limits. Physical examination revealed an 18-year-old male who appeared much younger (general appearance of the pre-pubertal boy) and shorter than the stated age (height of 130 cm, weight of 36 kg), with thin extremities and markedly protuberant abdomen, with the onset at the age of 11 after the diagnosis of diabetes. The abdomen was dull to percussion and diffusely tender to palpation. Tenderness was most pronounced in the right-upper-quadrant. A fluid wave was absent. Hepatomegaly was present, with the liver edge palpable 6 cm below the right costal margin.

His past medical history included long-standing type 1 diabetes mellitus (T1DM, for 7 years), celiac disease (for 7 years), severe protein-calorie malnutrition, pubertal delay and growth retardation since 2014, pulmonary tuberculosis in 2015, septic shock with the respiratory site of infection, pulmonary tuberculosis relapse with secondary nephrotic syndrome in 2019, and stage 3 essential hypertension. He was under therapy with enalapril 5 mg in the morning, long-acting glargine insulin at bedtime, and as part insulin at mealtimes. In addition, from discharge notes from the Pediatrics Department, we found that he had poor glycemic control since diagnosis and the failure of glycemic control and malnutrition were also due to the lack of adherence to diet for celiac dis-ease and diabetes and lack of compliance with recommended insulin regimen and glycemic monitoring. Of note, our colleagues in the Pediatrics Department provided home food adapted for celiac disease and according to the National Diabetes Program, he had access free of charge to insulin and glucose monitoring strips.

Laboratory evaluation showed metabolic acidosis: anion gap of 15 mmol/L, HCO_3 18.6 mmol/l, the glucose level of 476 mg/dl, serum lactate of 4.5 mmol/l, and ketonuria. Renal function was preserved, with no significant electrolyte disturbances. Other results showed glycated hemoglobin of 14.94%, elevated aspartate aminotransferase (AST) of 125 U/l, elevated alanine aminotransferase (ALT) of 106 U/l, decreased total protein of 5.62 g/dl, and decreased albumin of 3.1 g/dl, triglyceride levels were elevated to 301 mg/dl with total cholesterol of 237 mg/dl, meanwhile, total bilirubin, prothrombin time, international normalized ratio, erythrocyte sedimentation rate and C-reactive protein were within normal limits.

Abdominal ultrasound confirmed hepatomegaly and noted increased liver echogenicity, suggestive of hepatic steatosis. At this time, the differential diagnosis was between non-alcoholic fatty liver disease (NAFLD) and hepatic glycogenosis (HG).

To investigate the growth retardation and delayed puberty, thyroid function and reproductive hormones were performed, resulting in an elevated thyroid-stimulating hormone (TSH) level with a normal level of the free fraction of tetraiodothyronine hormone (FT4); low levels of luteinizing hormone (LH) 0.21 U/l (1.24–8.62 U/l); follicle-stimulating hormone (FSH) 0.60 mU/ml (1.26–7.4 mU/ml); normal levels of testosterone 0.14 ng/ml and sex hormone-binding globulin (SHBG) 20.5 nmol/l.

There was a general lack of compliance of patients with the insulin regimen and pre-scribed diet for diabetes and celiac disease. During this admittance, the education regarding the specific diet and insulin administration (fixed insulin doses and fixed carbohydrate intake due to his limited capacity to perform the calculation of insulin doses) was provided. Unfortunately, he did not acknowledge the necessity of further endocrine investigations and treatment, nor the importance of a follow-up program or adherence to recommendations for diabetes control. Thus, he was discharged with no confirmation of Mauriac syndrome or hope for a better diabetic outcome in the future.

Five months later, on the 5th of January 2022, he presented to the emergency department

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for complaints of nausea, vomiting, and epigastric pain, for the last 24 hours. Glycaemia at this presentation was 398.0 mg/dl, with a pH of 7.45 and an anion gap of 12 mEq/l. These results excluded the DKA as the etiology of gastrointestinal symptoms. After remission of symptoms under treatment, he was transferred to Diabetes Department for further investigations. At this second presentation, the poor diabetes control (HbA_{1c} was 13.65%), a moderate increase in transaminase levels, dyslipidemia, and abnormal thyroid function persisted. This time, we took a step forward to investigate our suspicion of Mauriac syndrome. Second liver ultrasonography was performed, also showing hepatomegaly and probable steatosis. Due to his history of T1DM and celiac disease, autoimmune hepatitis was also considered. Testing for anti-nuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial anti-bodies, and anti-liver-kidney microsomal antibodies were negative. Infectious causes of hepatitis, including viral hepatitis B or C were excluded by immunologic studies. Low levels of iron serum studies eliminated the suspicion of hemochromatosis. Upper endoscopy revealed gastric atrophic mucosa and cobblestone mucosa appearance in the second portion of the duodenum. Multiple biopsies were taken from the duodenum, describing moderate villous atrophy and crypt hyperplasia, confirming celiac disease, Marsh 3b stage.

Growth failure was estimated as -7.2 SD below the age and sex-matched mean. For pubertal status assessment, the Tanner scale was used, showing a stage 1. A further admittance in the endocrinology department confirmed type 1 diabetes and Mauriac syndrome as causes of the impaired growth and development of this patient.

Unfortunately, the patient did not undergo an image-guided percutaneous liver biopsy, to confirm our suspicion of Mauriac syndrome.

Again, at this presentation, we noted a general lack of compliance of patients with the insulin regimen and prescribed diet for diabetes and celiac disease. From heteroanamnesis (mother) we found that he often omitted the administration of the prandial insulin, frequently consumed sweets, and sugar-sweetened drinks as well as food containing gluten. During this second presentation, we performed again the therapeutic education on diet and insulin administration, underlying the link between growth failure, hepatomegaly, and poor glycemic control.

Discussion

The peculiarity of the case presented here is the onset of the features of Mauriac syndrome in childhood and their persistence through adolescence until adulthood despite the access free of charge to insulin analogs and tests for glucose monitoring. We found only one similar case of Mauriac syndrome reported in the literature in the past decades. In 2010, Madhu et al. [5] reported a case of 21-year-old men with uncontrolled type 1 diabetes treated with premixed insulin, growth retardation (height age 10.5 years and weight age 11 years), and protuberant abdomen with hepatic steatosis.

The clinical presentation of Mauriac syndrome includes short stature, delayed puberty, cushingoid appearance, dyslipidemia, protuberant abdomen, and hepatomegaly with transaminase elevation, in children or adolescents with poorly controlled type 1 diabetes [6]. Our patient displayed all the previously mentioned clinical features suggestive of Mauriac syndrome. He had a growth delay with short stature and sexual maturation corresponding to the pre-pubertal stage, as shown by the Tanner stage I. Delayed puberty or puberty dysfunction is frequently seen in patients with Mauriac syndrome diagnosed in pre-adolescence or adolescence [7]. Growth failure in Mauriac syndrome might be a consequence of elevated serum cortisol levels, as a counter-regulating hormone reactive to ketosis, associated with poor diabetes control, justifying the cushingoid appearance and delayed puberty [8]. This delay can also be a result of insulin deficiency, hyperglycemia itself, and decreased LH and FSH levels (as seen in Table 1), caused by the low gonadotropin-releasing hormone, secondary to cortisol release after glycemic excursion [6]. An additional cause is the growth hormone

Table 1. Laboratory investigations

	First Admission	Second Admission	Normal Values
Glucose	476	327	74-106 mg/dl
Glycated hemoglobin	14.94	13.65	4-6 %
Aspartate aminotransferase	135	74/108	< 50 U/L
Alanine aminotransferase	106	51/98	< 50U/L
Alkaline phosphatase		126	30-120 U/L
Gamma-glutamyl transpeptidase		64	<55 U/L
Total cholesterol	237	228	<200 mg/dl
Triglycerides	301	488	<150 mg/dl
Urea	18.06	27.71	17-43 mg/dl
Creatinine	0.42	0.46	0.67-1.17 mg/dl
Albumin	3.1	3.2	3.5-5.2 mg/dl
TSH	5.76	7.22	0.4-4 mg/dl
FT4	0.99	0.99	0.7-1.3 ng/dl
Right lobe	18	15	10-12.5 cm

TSH: Thyroid stimulating hormone; FT: Free Thyroxine.

resistance with reduced insulin-like growth factor-1 levels seen in Mauriac syndrome [9].

Hepatomegaly with increased transaminase levels, as seen in our patient, is considered a key feature of Mauriac syndrome and is due to hepatic glycogenosis [10, 11]. The pathogenic mechanism involved in this hepatic glycogenosis is not fully understood, but it seems that glycemic fluctuations, excessive insulin doses, or recurrent ketoacidosis episodes may be involved [10, 12]. Mauriac syndrome is considered a rare entity in the era of intensive insulin therapy; however, it is probably underdiagnosed because of the difficulty in differential diagnosis with nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) [13]. Current evidence shows that NAFLD is rare in T1DM, with a prevalence of less than 10% (lower than in the general population), unlike T2DM in which NAFLD has a much higher prevalence [13]. It is known that the diagnosis of hepatic glycogenosis consists in the exclusion of other causes of liver damage (infectious, metabolic, obstructive, and autoimmune disease), which we performed in our patient [10, 13, 14]. However, when encountering patients with T1DM with liver dysfunction, hepatomegaly, and fatty liver, clinicians should consider the diagnosis of Mauriac syndrome and a liver biopsy should be performed. In our patient, hepatomegaly and elevated liver enzymes were assumed to be a cause of intrahepatic glycogen deposition, in the context of the clinical appearance supporting this diagnosis, but a liver biopsy was not performed to confirm it.

The mainstay of treatment for hepatic glycogenosis, delayed growth, and development and other features of the Mauriac syndrome is strict control of glucose levels, with an excellent prognosis with improved glycemic control [15, 16]. Even though the glycated hemoglobin was slightly improved on the second admission, taking into consideration our patient's daily hypoglycemic episodes seen during hospitalization, it is improper to expect an improvement in his insulin management after discharge, despite explanation regarding his condition and the possibility to reverse it by proper glycemic control.

Conclusions

We wish to highlight the key clinical signs in poorly controlled type 1 diabetes (short stature,

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growth delay, cushingoid appearance, protuberant abdomen, and hepatomegaly) to avoid Mauriac syndrome remaining misdiagnosed. Adequate management of glucose and insulin levels can result in complete remission of clinical, laboratory, and histological abnormalities. By illustrating unique elements of this presentation, we aim to aid pediatricians, but not only, in an earlier diagnosis for a better outcome.

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Conflicts of Interest

A.R. reports support from Sanofi. A.Z and A.B have nothing to disclose.

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