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Mauriac Syndrome: Case Report and Review of the Literature

Mauriac Sendromu: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

This is a case report of a young male with poorly controlled type 1 diabetes mellitus who presented with the clinical features of diabetic ketoacidosis. Once the patient was stabilized, he was examined for hepatomegaly and elevated liver enzymes. Along with the other clinical features, the patient was diagnosed as a case of Mauriac Syndrome. Mauriac Syndrome, initially described by Mauriac in 1930, is one of the causes of hepatomegaly and elevated liver enzymes in poorly controlled diabetic patients. However, hepatomegaly, growth retardation and other clinical features of the syndrome have been found to be reversible with optimization of insulin therapy. In patients with poorly controlled diabetes, Type 1 diabetic patients must be closely observed for sexual maturation and growth. After optimal therapy has been given, close follow-up is essential to observe the regression of clinical features.
Keywords: Mauriac syndrome, hepatic glycogenosis, type 1 diabetes mellitus.

Özet

Diyabetik ketoasidozun klinik bulgularıyla prezente olan kötü kontrollü tip 1 diabetes mellitus tanılı genç bir erkek hastayı sunuyoruz. Hasta stabilize edildikten sonra, hepatomegali ve artmış karaciğer enzimleri açısından incelendi. Diğer klinik bulgular eşliğinde, hastaya Mauriac sendromu tanısı koyuldu. Mauriac sendromu ilk olarak 1930'da Mauriac tarafından tanımlanmıştır ve kötü kontrollü diyabetik hastalardaki hepatomegali ve karaciğer enzim yüksekliği sebeplerinden biridir. Hepatomegali, büyüme geriliği ve sendromun diğer klinik bulgularının insulin tedavisinin optimizasyonu ile geri dönebildiği bilinmektedir. Kötü kontrollü diyabet hastalarında, hastalar cinsel matürasyon ve büyüme gelişme açısından yakından izlenmelidir. Optimal tedavi verildikten sonra, klinik bulguların regresyonunu izlemek açısından yakın takip elzemdir.
Anahtar kelimeler: Mauriac sendromu, hepatik glikogenoz, Tip 1 diabetes mellitus

Introduction

Hepatomegaly and elevated liver enzymes in diabetic patients must be looked for in an orderly manner. Although the most common cause of elevated liver enzymes in diabetic patients is 'non-alcoholic fatty liver disease (NAFLD)', glycogenic hepatopathy is one of the other causes. Glycogenic hepatopathy may either exist alone or in combination with other features, as a part of Mauriac Syndrome. A case of Mauriac Syndrome in a patient with poorly controlled type 1 diabetes mellitus (DM) has been presented in the following case report.

Case

A 20-year-old male with type 1 DM was referred to the hospital with complaints of diarrhea, nausea, and vomiting since a few

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days. The stool of the patient was brownish and did not contain mucus or blood. Fever, weakness, and anorexia were some of the other symptoms. The patient also complained of morning fasting hypoglycemia episodes for a long time. The patient was diagnosed with type 1 DM in childhood and had suffered from the same since last 11 years; he also presented with diabetic ketoacidotic coma. The patient has been on intensive insulin regimen since the time he was diagnosed with DM. No other autoimmune diseases or complications of diabetes could be seen in the patient. The patient was not on any other medication.

Physical examination revealed that the patient had body temperature 37.6 °C, pulse rate was found to be 138 beats/min, blood pressure was noted to be 86/40 mmHg, body weight was 45 kg and height was 155 cm. He had protuberant abdomen, moon face, and diminished beard. The liver was non-tender, has smooth margins and was palpable at 12 cm from the right costal margin at the midclavicular line. Splenomegaly and ascites were not found. No palmar erythema, spider angiomata, leg edema, petechia or purpura were found. Examinations of the other systems did not reveal any remarkable findings.

Laboratory analysis showed that venous plasma glucose was 348 mg/dL, urine ketone was moderately positive; arterial blood gas analysis was observed to be compatible with metabolic and lactic acidosis. Biochemical analysis revealed increased ALT (184 U/L), AST (167 U/L), gamma-GT (180 U/L) and ALP (140 U/L) levels (Table 1). The patient was diagnosed with diabetic ketoacidosis and appropriate fluid, electrolyte, and insulin protocol were followed. Intensive insulin regimen and diet therapy were initiated once the patient was stable. During the follow up of the patient, serum calcium, and phosphorous levels were found to be more than the upper limits of normal. The reason for these increments could not be detected and the patient was followed up further.

Ultrasonography of the abdomen revealed hepatomegaly (vertical length 175 millimeters) and increased liver parenchymal echogenicity compatible with grade 1 steatosis; the kidneys were found to be normal in terms of size and echogenicity. Serological findings (positive anti-HBs 922.07 mIU/mL, and anti-HBc; negative HBs) suggested recovery from hepatitis B infection. Other viral and parasitic markers were found to be negative (anti-HAV, anti-HCV, anti-HIV 1, anti-HIV 2, anti-rubella IgM, anti-CMV IgM, EBV VCA IgM, parvovirus B19 IgM, anti-toxoplasma IgM and IgG). Autoimmune hepatitis markers such as antinuclear antibody, anti-smooth-muscle antibody, anti-liver-kidney-muscle, antimitochondrial antibody were negative. Thus, any possible infectious hepatitis, autoimmune hepatitis, and primary biliary cirrhosis were excluded. Ophthalmological examination revealed no findings of Kayser-Fleischer ring or diabetic retinopathy. Ferritin (90 ng/mL) and alpha$_1$-antitrypsin (1.1 g/L; normal range 0.9–2) were found to be in the normal range. No corresponding signs or symptoms of amyloid organ infiltration or Gaucher disease were seen.

Possible diagnoses included nonalcoholic steatohepatitis, primary (congenital) glycogen storage disease, and secondary glycogen storage disease. To demonstrate hepatic glycogen or fat deposition, liver biopsy was performed. The liver biopsy revealed PAS-positive granules in enlarged hepatocytes, indicating the presence of glycogen deposition. The presence of combined clinical findings such as hepatomegaly, elevated liver enzymes, hepatic glycogen deposition, hyperlipidemia, Cushingoid features, and short stature led to the diagnosis of Mauriac syndrome probable. On the basis of this diagnosis, the hormonal analysis was also performed. Total testosterone was found to be 126 ng/dL (262 to 1593), LH was 0.86 mIU/mL (0.8 to 7.6), FSH was 2.99 mIU/mL (0.7 to 11.1), IGF–1 was 120 ng/mL (182 to 780), cortisol was 30.2 mcg/dL (5.0 to 25) and ACTH was observed to be 21.7 pg/mL (0 to 46). Radiographical examination of the left wrist revealed that the bone age was 14. The laboratory and radiological findings demonstrated hypogonadotropic hypogonadism and growth retardation, suggesting Mauriac syndrome. Genetic analysis was also performed to exclude congenital glycogen storage disease type 1 (GSD–1). Heterozygote mutation (17q21, p.R83C) in glucose-6-phosphatase gene was found in the patient. Although it is known that the carriers of GSD–1 are asymptomatic, the existence of GSD–1 carrier status may contribute to hepatic glycogen deposition in a patient with Mauriac syndrome.

Table 1. Biochemical test results of the patient.

Test	On admission	1 day later	12 days later	Reference value
Glucose	292	57	276	74–106 mg/dL
Urea	44	7	39	17–43 mg/dL
Creatinine	1.3	0.6	0.7	0.8–1.3 mg/dL
Uric acid		3.6	4.7	3.5–7.2 mg/dL
Cholesterol		217	302	110–199 mg/dL
Triglyceride		208	268	30–199 mg/dL
HDL-cholesterol		34	52	40–85 mg/dL
LDL-cholesterol		141	196	62–129 mg/dL
AST	167	160	55	1.0–35 U/L
ALT	184	132	64	0–45 U/L
ALP		180	221	30–120 U/L
Gamma-GT		140	120	0–55 U/L
LDH		264	239	0–248 U/L
CK	27	33	21	0–171 U/L
T.Bilirubin	0.5	0.5	0.32	0.3–1.2 mg/dL
D.Bilirubin	0.1	0.1	0.06	0.0–0.2 mg/dL
Protein		5.77	7.4	6.6–8.3 g/dL
Albumin		3.6	4.5	3.5–5.2 g/dL
Globulin		2.17	2.9	2.3–3.5 g/dL
Na	138	138	137	136–145 mmol/L
K	3.7	3.8	4.64	3.6–5.1 mmol/L
Cl	95	102	95	96–110 mmol/L
Ca	9.9	9.1	10.9	8.8–10.6 mg/dL
P		3.1	5.4	2.5–4.5 mg/dL
Ferritin		90		10–160 ng/mL
HbA_{1c}		10.34		4–6%

Discussion

Glycogenic hepatopathy was first described by Mauriac (1) in 1930 as "hepatic glycogenosis", in children affected with brittle diabetes,

Cushingoid features, poor growth, and hyperlipidemia. Hence the syndrome was named as Mauriac syndrome. Later then, the reports showed the presence of hepatic glycogenosis without other features of the syndrome (2).

The pathophysiologic process of glycogenic hepatopathy involves two components: hyperglycemia and overinsulinization.[2] In patients with poorly controlled type 1 DM, hyperglycemia increases the need for insulin. When insulin is administered to the patient in higher amounts, more quantities of active glycogen synthase are activated by the insulin. Increased activation of enzyme promotes hepatic glycogen storage by conversion of glucose-1-phosphate to glycogen. Because the entry of glucose into the liver via GLUT–2 mechanism is insulin independent, hyperglycemia itself also initiates glycogen synthesis. In some instances, glycogen could also be stored in kidneys causing nephromegaly. Although the most well-known cause of acquired glycogenic hepatopathy is uncontrolled type 1 DM, uncontrolled type 2 DM and use of corticosteroids may also cause this type of glycogenic hepatopathy. In glycogenic hepatopathy, hypercortisolism also contributes to glycogen storage in the liver (3), as was evident in this patient. Hypercortisolism also causes delay in sexual maturation and growth in patients with Mauriac syndrome (3).

Glycemic fluctuations may also cause hepatic glycogenosis, due to the discrepancy between insulin and glucose levels in the blood. The most common cause of these fluctuations is uncontrolled diabetes mellitus. This patient also exhibited glycemic excursions in the hospital. These two clinical features caused the glycogenic hepatopathy in the patient. Resnick et al. reported Dumping syndrome as a cause of acquired glycogenic hepatopathy, in a 2-year-old male patient who had undergone fundoplication and was fed by gastrostomy; he presented no evidence of congenital glycogen storage disease, diabetes mellitus, or corticosteroid use (4). From the point of view that glycemic oscillations in Dumping syndrome could lead to glycogenic hepatopathy, the authors suppose that glycemic undulations in diabetic gastroparesis could also result in glycogenic hepatopathy. There are no studies in the literature depicting the relationship between diabetic gastroparesis and acquired glycogenic hepatopathy in diabetic patients.

It is important to distinguish Nonalcoholic Steatohepatitis (NASH) from glycogenic hepatopathy. NASH warrants weight loss, correction of hyperglycemia, improvement of hypertriglyceridemia and therapy using insulin-sensitizing agents and ursodeoxycholic acid (5). However, in glycogenic hepatopathy, glycemic control by adequate intensive insulin regimen reverses the condition of glycogen deposition and hepatomegaly. Although glycogenic hepatopathy does not progress to cirrhosis (6-8). NASH is an established cause of cirrhosis and is frequently diagnosed worldwide (5). The chief means of distinguishing between NASH and glycogenic hepatopathy is a liver biopsy. However, in case glycogenic hepatopathy is highly suspected, the empirical therapy for regulation of glycemic control could be initiated and biopsy may not be a necessity. However, both, glycogenosis and steatosis may exist simultaneously in the same patient as reported in some cases (9). Whenever a type 1 DM patient presents with hepatomegaly or elevated serum liver enzymes, the differential diagnosis should include the classic causes of liver damage and hepatomegaly. However, insulin-reversible hepatic glycogenosis should be thought in priority, especially in the patients with uncontrolled type 1 diabetes. Insulin-reversible hepatic glycogenosis is the most common cause of hepatomegaly and raised serum liver aminotransferase levels in children and adolescents with type 1 DM (10). Nevertheless, elevated liver enzymes do not predict the presence or the extent of glycogenosis (6). The other major cause of hepatomegaly in diabetic patients is steatosis, and thus the distinction between steatosis and glycogenosis is important and obligatory. Ultrasonographic examination cannot reliably distinguish between these two conditions, as is evident in the present patient, where ultrasonography of abdomen showed increased echogenicity compatible with grade 1 steatosis, but a liver biopsy revealed only glycogen storage. For this reason, the distinction between steatosis and glycogenosis in a patient with uncontrolled diabetes and hepatomegaly obligates liver biopsy (6). However, according to some authors liver biopsy should be reserved for patients with persistently elevated liver enzymes despite metabolic control (11).

In patients with Mauriac syndrome, all the clinical features regress with optimum insulin therapy and strict control of blood glucose levels. During follow up, in patients with glycogenic hepatopathy, hepatomegaly and elevated liver enzymes generally return to normal with tight metabolic control of four weeks (10,12). In this patient, hepatomegaly and elevated liver enzymes returned to normal after four weeks of discharge. In a patient with type 1 DM, if hepatomegaly persists for a period longer than four weeks, other reasons must be investigated (12). In another case report it was seen that with optimum insulin therapy, the clinical and biochemical manifestations of three patients with glycogenic hepatopathy reversed within two weeks (3).

Other features of the syndrome also regress with insulin treatment, though it takes more time. One of the signs of Mauriac syndrome is growth failure. Mauras et al. investigated the mechanisms involved in growth failure in two patients with Mauriac syndrome (13). No hypothalamic-pituitary dysfunction was observed in them. However, in the patient involved in the present study, both decreased IGF–1 levels and hypercortisolism led to growth failure. Growth failure also regresses with adequate insulin treatment in patients with Mauriac syndrome (14). For this reason, growth and pubertal maturation in patients with type 1 DM must be monitored closely, with optimal therapy.

Pubertal delay in Mauriac syndrome can also be reversed by providing optimal insulin therapy. Traisman et al. followed up a female patient diagnosed with Mauriac syndrome for 22 years and found that although delayed sexual development was present she demonstrated two successful pregnancies (15). The laboratory results of the patient involved in the present case revealed hypogonadotropic hypogonadism. An aggressive treatment with insulin may result in the deterioration of retinopathy and nephropathy in patients with Mauriac syndrome (14).

In type 1 DM patients indicated for pancreatic transplantation, transplantation has been found to improve glycemic control and reduce diabetic complications; although a number of complications belonging to transplantation itself may ensue. Whether or not

the pancreatic transplantation is efficient in Mauriac syndrome has not yet been well established. Maia et al. reported that the clinical and biochemical derangements of a patient with Mauriac syndrome had improved after pancreatic transplantation (16). Hence, pancreatic transplantation may be considered as an option for patients with Mauriac syndrome.

The pathophysiological process could ensue at any time after diagnosis of type 1 DM (6,17). In the present patient, hepatic glycogenosis was determined 11 years after the diagnosis of type 1 DM. However, a case report of two patients with type 1 DM revealed a clinical picture of hepatic glycogenosis with the presentation of type 1 DM, after supraphysiological doses of insulin were administered (17). Though hepatic glycogenosis has classically been described in patients with type 1 DM, it may also be diagnosed in type 2 diabetic patients who are using higher quantities of insulin or are incompatible with diet. Another case report of glycogenic hepatopathy in a patient with type 2 diabetes mellitus was published (18).

In cases of glycogenic hepatopathy, serum liver enzymes are mild to moderately elevated. In the patient involved in the present case report, alanine aminotransferase and aspartate aminotransferase levels were elevated four and a half times the upper limit of normal. Torbenson et al. showed that in patients with glycogenic hepatopathy, the level of liver transaminases could be dramatically elevated, up to ten times the upper limit of normal (7). Liver synthetic function is generally preserved in patients with glycogenic hepatopathy as was event in the patient involved in the present case report (6).

Hypoglycemia may occur in patients with type 1 DM, because of the course of diabetes, aggressive treatment, or blunted counterregulatory hormone response. When the episodes of hypoglycemia are observed in a patient with type 1 DM and hepatomegaly, congenital glycogen storage diseases(GSD) should also be considered as differential diagnoses. In this patient, GSD1a was considered as a differential diagnosis, owing to the existence of hypoglycemic episodes, hepatomegaly, lactic acidosis, growth retardation, hyperlipidemia, and hepatic glycogenosis. Lei et al. showed that most frequent mutations of G6P gene are R83C (37%) and Q347X (22%) as observed in 70 patients previously diagnosed as GSD1a by the lack or greatly reduced activity of G6Pase activity in liver biopsy specimens. Including other less common mutations in that study, 11 of 70 patients carried only one mutant allele; one of the Jewish patients was heterozygous for R83C mutation (19). Accordingly, in the patient, in the present case report, whether heterozygous R83C mutation would contribute to hepatic glycogenosis and other clinical features is debatable. The authors agree that the clinical features of the patient in the present case report were compatible with Mauriac syndrome and associated secondary hepatic glycogenosis owing to hepatomegaly, lactic acidosis and the lack of neonatal history of hypoglycemia and initiation of clinical features with puberty.

Tomihira et al. reported the occurrence of hepatic glycogenosis in a female with type 1 DM admitted with diabetic ketoacidosis (20). Due to recurrence of marked hepatomegaly and elevated liver transaminases with the concurrence of hypoglycemic episodes, they supposed the partial deficiency of liver glycogen phosphorylase activity and analyzed the PYGL gene. The nucleotide sequence of the gene was observed to be heterozygous for substitutions at positions Asp339 on exon 9 and Ala703 on exon 17. They concluded that the structure of PYGL coding sequence in that patient was unlikely to cause liver glycogenosis. Therefore, in patients with diabetes and hepatic glycogenosis, the clinical decision of whether the glycogenosis is primary or secondary must be done at first. This could be followed by genetic analysis in case, the history supports congenital glycogen storage disease and clinical suspicion is high.

Conclusion

As soon as hepatomegaly and elevated liver enzymes are detected in diabetic patients, detailed history and physical examination must be carried out. Glycogenic hepatopathy should be considered, especially in patients with poorly controlled type 1 DM. If other clinical features accompany, Mauriac syndrome may be suspected.

In a diabetic patient with glycogenic hepatopathy or Mauriac syndrome, the clinical features regress with optimization of insulin therapy, and the follow-up of the patient in regard to glycemic control and other clinical features is obligatory. In patients with type 1 DM, growth and pubertal maturation should be closely monitored, as growth failure and pubertal maturation delay could be the presenting features of Mauriac Syndrome.

Hence, as in all diabetic patients, patient education is essential, especially for the reversibility of clinical features with optimal insulin therapy, so is in Mauriac Syndrome.

Author Contributions

Concept: Ömercan Topaloğlu, Design: Sibel Demiral Sezer, Data Collection or Processing: Derya Akarken, Analysis or Interpretation: Ömercan Topaloğlu, Literature Search: Ömercan Topaloğlu, Writing: Ömercan Topaloğlu.

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