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Review Article

Mauriac Syndrome: A Comprehensive Review of a Rare Complication of Poorly Controlled Type 1 Diabetes Mellitus

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ABSTRACT

Mauriac syndrome (MS) is a rare complication of type 1 diabetes mellitus (T1DM) in children and adolescents. It is caused by consistently insufficient glycemic control and manifests as hepatomegaly with growth retardation. It is unclear what variables lead to delayed puberty and delayed growth in MS. Since the discovery of insulin analogues and long- and intermediate-acting insulin, the distinct clinical signs and symptoms of MS have rarely been reported. Lack of insulin as a growth factor, hypercortisolism, and insufficient glucose in tissues can all play a part in the multifactorial pathophysiology of development and pubertal delay. Mauriac syndrome can be characterized by short stature, moon facies, hepatomegaly, protuberant abdomen, pubertal delay, proximal muscle wasting, reduced joint mobility, and nephropathy/retinopathy. These changes are linked to the duration of poor glycemic control and microvascular consequences. To achieve optimal glycemic regulation, the clinician needs to have a high index of suspicion about Mauriac syndrome. This review aims to highlight a comprehensive review of a rare complication of poorly controlled type 1 Diabetes Mellitus.

Keywords: Complication, Glycemic control, Glycogenic hepatopathy, Mauriac syndrome, Type 1 diabetes

INTRODUCTION

Mauriac syndrome (MS) is a rare complication of type 1 diabetes mellitus (T1DM) in children and adolescents. It is caused by consistently insufficient glycemic control and manifests as hepatomegaly with

growth retardation. Patients with MS experience periods of extended hyperglycemia, in which glucose is converted to glycogen in the absence of insulin, resulting in glycogen accumulation in their hepatocytes. It is unclear what variables lead to delayed puberty and delayed growth in MS [1].

History of Mauriac syndrome

The term "Mauriac syndrome" has been replaced by "hepatic glycogenosis" or "hepatocyte glycogen overload [2]." Mauriac first characterized the syndrome in 1930 in children with type 1 diabetes who presented with hepatomegaly, abdominal distension, and failure to thrive [2]. Since the discovery of insulin analogues and long- and intermediate-acting insulin, the distinct clinical signs and symptoms of MS have rarely been reported [3].

Incidence and Gender dominance

The majority of MS cases frequently involve adolescents with the same gender ratio [3]. The true incidence and frequency of glycogenic hepatopathy are unclear; 62% of the recorded cases are female patients, showing a small female predominance; the majority of cases occur in adolescence [4,5].
A study conducted by Zalzala et al. found that the prevalence of type 1 diabetes mellitus among primary Iraqi schoolchildren in Baghdad city was 159 per 100,000 [6], in Basra City was 5-9.99/100,000 each year and was increasing from 2012 to 2016, it was in 2016 much higher, at 87 per 100,000 [7]. Similarly, in Al-Nassiryah City, the incidence has been increasing during the last five years [8]. MS incidence in Iraq has not been documented; however, it is important to have national/regional diabetes registries available to promote diabetes research and offer reliable data on the incidence of T1DM comorbidities, including MS.

Risk factors of Mauriac syndrome

Mauriac Syndrome primarily affects children and adolescents with poorly managed T1DM [9]. It can occur in poorly controlled type 1 or type 2 diabetes individuals [10].

Pathophysiology

The pathogenesis of Mauriac syndrome is still unclear. It appears to be linked to both high insulin levels and hyperglycemia episodes. Insulin inhibits glucose-6-phosphatase and stimulates glycogen synthase and glucokinase, leading to the overaccumulation of circulating glucose in the form of intrahepatic glycogen through hyperstimulation of glycogenesis and suppression of glycogenolysis; these mechanisms play a role in hepatic glycogenosis when insulin overconsumption occurs concurrently with hyperglycemic periods [2]. MacDonald et al. discovered a mutation in the catalytic subunit of liver glycogen phosphorylase kinase in a Mauriac syndrome patient who had substantial hepatomegaly and growth failure [11]. The enzyme that catalyzes the first stage of glycogen degradation is glycogen phosphorylase, which is triggered by glycogen phosphorylase kinase. When combined with hyperglycemia, a mutant glycogen metabolism enzyme can directly inhibit glycogen phosphorylase, preventing glycogenolysis and resulting in the hepatomegaly seen in MS [11]. Thus, the syndrome cannot be induced solely by hyperglycemia or a faulty enzyme; rather, it

requires the combination of a mutant glycogen metabolism enzyme and chronic hyperglycemia [11]. The histopathologic features of liver biopsy are characterized by large glycogen-laden hepatocytes with no evidence of inflammation, necrosis, fibrosis, or steatosis [3,12]. Insulin deficiency as a growth factor, hypercortisolism, and inadequate glucose availability in tissues can all contribute to the complex pathophysiology of developmental and pubertal delay [2].

Clinical features of Mauriac syndrome

Mauriac syndrome can be characterized by short stature, moon facies, hepatomegaly, protuberant abdomen, pubertal delay, proximal muscle wasting, reduced joint mobility, and nephropathy/retinopathy. These changes are linked to the duration of poor glycemic control and microvascular consequences [13,14].

The presence or absence of obesity distinguishes two subgroups of Mauriac syndrome. Poor glycemic regulation and glycemic variability in the obese type of the syndrome result in considerable and extensive swings between hyper- and hypoglycemia, implying a pattern of over- and under-insulinization. Individuals with the non-obese version of the illness had inadequate insulin delivery and no prior history of fluctuating hypoglycemia and ketoacidosis [3].

Priyadarshini et al. identify adolescent age, low socioeconomic position, and poor glycemic management as important indicators of MS development [15]. When Mauriac syndrome presents in children and adolescents with T1DM, other autoimmune illnesses, particularly celiac disease, must be eliminated as these conditions can also cause growth failure, delayed puberty, and poor glycemic control. Excluding them is essential because their clinical features may mimic Mauriac syndrome, and appropriate management of these autoimmune disorders (such as a gluten-free diet in celiac disease) can lead to significant improvement in growth and metabolic outcomes [15].

Differential Diagnosis

In the era of intense insulin therapy, MS is considered as an uncommon condition; nonetheless, it is likely underdiagnosed because of the difficulties in distinguishing it from nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) [16]. According to published data, NAFLD is less common among T1DM patients than in the general population, with a prevalence of less than 10% [16].

In contrast, NAFLD is much more prevalent in T2DM patients [16]. Moreover, it is generally stated that ruling out alternative etiologies of liver damage, including autoimmune, metabolic, obstructive, and viral diseases, is an essential step in diagnosing hepatic glycogenosis [16 - 18].

Laboratory Abnormalities in MS

Glycogenic hepatopathy, characterized by hepatomegaly and aberrant liver enzymes, is one of the hallmarks of Mauriac syndrome [19].

- **Liver enzymes abnormalities:** Although the liver function panel is normal, MS patients may experience increased liver enzymes and severe transaminase flare-ups of up to 2000-4000 U/L. Glycogenic hepatopathy in MS is

distinct from nonalcoholic fatty liver disease (NAFLD), which is defined by a modest to moderate rise in liver enzymes (less than five times the upper limit of normal range). NAFLD's liver damage can cause fibrosis and cirrhosis, while MS's glycogenic hepatopathy cannot [20].

- **Histopathology:** A transcutaneous ultrasound-guided liver biopsy is considered the gold standard for verifying the clinical diagnosis of MS. The histological hallmarks of the condition include big, swelling, glycogen-laden hepatocytes and glycogenated nuclei without significant fatty alterations, inflammation, fibrosis, or lobular necrosis [3].

- **Lactate levels :** The persistent rise of serum lactate levels is a well-documented feature of Mauriac syndrome. Lactic acidosis can be caused by end-organ failure, peripheral tissue hypoperfusion, or hepatic lactate clearance malfunction. There is currently uncertainty about the reason of Mauriac syndrome's prolonged lactatemia [19].

- **Radiological abnormalities in MS**: Because of glycogen accumulation in the liver, an abdominal CT scan for MS patients with glycogenic hepatopathy showed increased hepatic CT attenuation. Furthermore, Gradient-dual MRI is a powerful, noninvasive approach of identifying such hepatopathy [20].

Treatment and Prognosis

- **Improved Glycemic Control:** Better blood glucose control is part of MS treatment, and it often results in hepatomegaly remission and liver enzyme normalization. For such patients, continuous insulin delivery and continuous glucose monitoring may be the best line of action to improve clinical results [12].

There is considerable evidence that those with suboptimal glycemic management have a fall in height velocity, which leads to their significantly reduced stature in MS, whereas those with great glycemic control maintain their height advantage. The growth hormone (GH) and insulin-like growth factors (IGFs) axis are primarily regulated by insulin; regular insulin concentrations and an appropriate supply of insulin are required to maintain normal serum concentrations of IGFs and IGF-binding proteins and sustain growth [21]. Physiological insulin levels have improved as a result of many daily injections, insulin analogs, and new technologies such as insulin pumps and continuous glucose monitoring. These adjustments have enhanced GH/IGF levels and height results [21].

- **Nutritional Support:** In addition to keeping blood glucose levels stable, good nutritional assistance is essential for controlling T1DM and preventing MS. T1DM is a chronic and burdensome illness that impacts growth, so it is vital to frequently examine the nutritional health of young children [22].

However, despite the availability of carbohydrate counting strategies to improve glycemic control, many teenagers with type 1 diabetes continue to struggle to maintain appropriate blood glucose levels, leading to the maintenance of MS in some cases [23]. It's crucial to prioritize patient adherence to insulin dosing, rather than just increasing insulin dosages in response to hyperglycemia caused by poor dietary habits.

Monitoring and Support: Early detection, appropriate multidisciplinary care, and regular review may lead to a better prognosis because the illness is likely to be reversible [1]. T1DM, as a chronic condition, can lead to long-term complications like retinopathy, nephropathy, limited joint mobility, and cognitive impairment [13, 14, 24]. This underscores the importance of a multidisciplinary approach to care—addressing not only features of Mauriac syndrome but also these related complications in children with poorly controlled T1DM. The table below summarizes reported cases of Mauriac syndrome over the past decade, highlighting their clinical features and outcomes.

Table 1: Summary of some case reports of MS that had been reported in last 10 years in pediatric age group [3, 14, 20, 25-30].

Ref.	Age/Sex F: (female), M: (male), yrs: (years).	Duration of diabetes	Clinical features	Follow-up
Oeschgef (2014) [25]	11 yrs/F, 10 yrs/M, 14 yrs/F, 14 yrs/F 13 yrs/F	2 years, 3 years, 11 years, 8 years, 10 years	Hepatomegaly, elevation of triglycerides and aminotransferases.	First 2 patients: unknown resolution, second 2 patients: resolution poor, last patient: resolution
Butts (2014) [26]	13 yrs/F	2 years	Hepatomegaly, elevation of aminotransferases	Unknown
Chandel (2017) [27]	12 yrs/F	5 years	Hepatomegaly, elevation of aminotransferases	Resolution
Al Sarkhy (2017) [28]	6 yrs/F	4 years	Hepatomegaly, elevation of aminotransferases	Resolution
Thakkar (2017) [14]	16 yrs/M	13 years	Moon-like face, protruded abdomen. Delayed secondary sexual characteristics for his age, elevation of aminotransferases.	Resolution
Alenazy (2020) [20]	16 yrs/F	4 years	Hepatomegaly, elevation of aminotransferases.	She is persistently symptomatic with hepatomegaly and abnormal liver enzymes.
Siddhanta (2021) [3]	15 yrs/F	2 years	Hepatomegaly, elevation of aminotransferases, short stature, delayed puberty, dyslipidemia.	Resolution
Kale (2024) [29]	13 yrs/F	6 years	Growth failure, hepatomegaly with raised liver enzymes, and delayed puberty.	Her transaminases normalized, hepatomegaly was persistent.
Rahman (2024) [30]	7 yrs/M	4 years	Growth failure, hepatomegaly, delayed puberty.	Resolution

CONCLUSION

Mauriac syndrome is a rare complication of type 1 diabetes. It is characterized by hepatomegaly and severe transaminase flare-ups; however, it can be treated with proper glycemic management. To establish effective glycemic management, the doctor must have a high level of suspicion for MS.

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