

Old syndrome–new approach: Mauriac syndrome treated with continuous insulin delivery

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Mirjana Kocova  and Liljana Milenkova

Abstract

Mauriac syndrome has rarely been reported in children and adolescents with a poorly controlled diabetes mellitus type 1. However, it still occurs despite the worldwide improvements of metabolic control. The risks have not been elucidated. We present a 13.5-year-old boy with a typical clinical presentation of Mauriac syndrome consisting of growth delay, cushingoid appearance, hepatomegaly, and delayed puberty. A stepwise correction of glycemic control was introduced using continuous insulin delivery. All symptoms improved during the 2.5-year follow-up. No retinopathy occurred. This patient with Mauriac syndrome followed with continuous glucose monitoring and treated with continuous insulin delivery, resulting in no retinopathy after 2.5 years of follow-up. We suggest that this approach should be recommended in patients with Mauriac syndrome.

Keywords

Mauriac syndrome, continuous insulin delivery, follow-up

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Introduction

Mauriac syndrome is a rare complication of poorly controlled diabetes mellitus type 1 (DM1) characterized by hepatomegaly, growth failure, delayed puberty, and cushingoid features. It appears more frequently in adolescents; however, young children and adults can also be affected. Mauriac syndrome is probably caused by a combination of factors, including inadequate glucose utilization in tissues and decreased insulin-like growth factor-1 (IGF-1) and growth hormone levels or resistant/defective hormone receptors; however, the precise etiology has still not been elucidated.^{1–3} It is not known why it is not more common in children with poorly controlled DM1, but appears rather sporadically.⁴

The generally accepted therapeutic approach is intensified multiple insulin injection therapy; however, the fast improvement of the metabolic control induces rapid appearance of retinopathy or aggravates existing retinopathy.^{5,6}

Here, we present a patient with a Mauriac syndrome who was transferred to continuous insulin delivery resulting in a slow and step-by-step improvement of the metabolic control.

The analysis and the treatment of the patient have been carried out in accordance with the Declaration of Helsinki. Informed consent from the mother and assent from the patient were obtained for publishing the case report together with the photos.

Case

A 13.5-year-old boy with DM1 was referred for hospitalization due to stunted growth, cushingoid appearance, and high HbA1c level. He was diagnosed with DM1 at the age of 5 years, initially in a state of diabetic ketoacidosis. His growth at diagnosis was at the 25% which was normal according to the parents' height. Regular education for multiple injection therapy (insulin aspart and insulin detemir) and blood glucose monitoring was conducted. After 2 years of appropriate control, the contact with the family was lost due to the divorce of the parents. The boy, then managing his diabetes on his own, followed the diet recommendations intermittently, did not count carbohydrates and received inappropriate amounts of insulin. His glucose measurements were rare and very variable. However, he was never hospitalized due to overt ketoacidosis or severe hypoglycemia.

Physical examination showed short stature at -0.1% (-3.3 standard deviation (SD) below the mean), no central puberty, cushingoid appearance with a weight at 22%, and

University Pediatric Clinic, Skopje, Republic of Macedonia

Corresponding Author:

Mirjana Kocova, University Pediatric Clinic, 1000 Skopje, Republic of Macedonia.

Email: mirjanakocova@yahoo.com



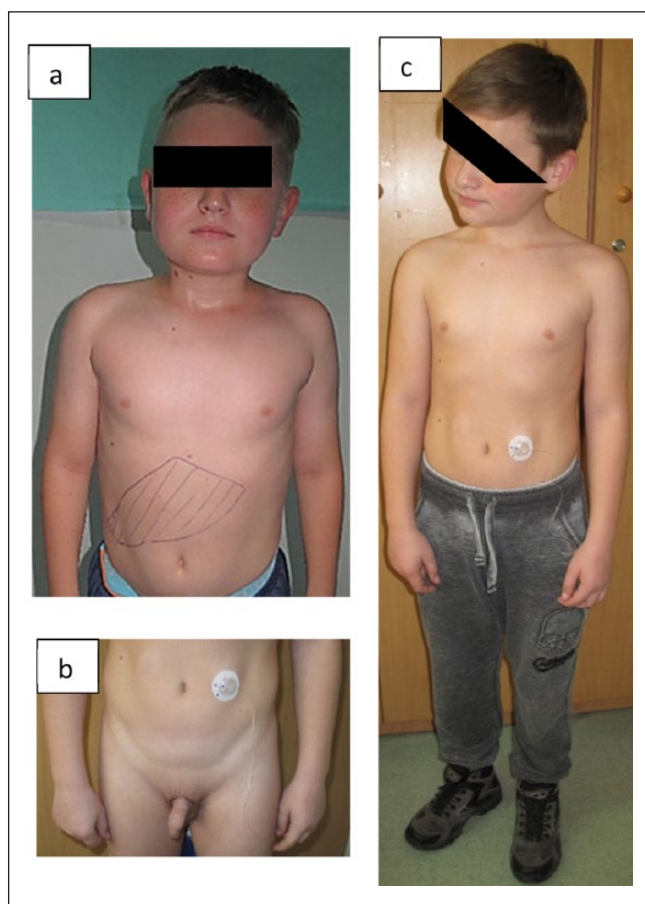


Figure 1. (a) Patient at diagnosis with cushingoid face and torso and hepatomegaly. (b) Delayed puberty at diagnosis (insulin pump is attached to the abdomen). (c) The boy 1 year after continuous insulin delivery—normal appearance, no hepatomegaly.

liver enlargement (6 cm below the right costal margin; Figure 1). His bone maturation was delayed (-4 SD). He had high HbA1c (11.9%–105 mmol/mol), nonexistent C-peptide (<0.10 ng/mL), and his cortisol and lipid levels were normal. Thyroid hormones were within the normal range, as well as the results of the stimulating luteinizing hormone-releasing hormone (LH-RH) test (peak values for follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were 1.82 and 4.80 mIU/mL, respectively). All abnormal analyses are presented in Table 1. Abdominal ultrasonography showed enlarged liver of 19/24 cm (midclavicular/midhepatic line) with a normal structure. Continuous glucose monitoring (CGM) showed severe peaks of hyperglycemia but also large variations with hypoglycemic periods (Figure 2(a)). The ophthalmological examination was normal.

These findings were consistent with Mauriac syndrome. The therapeutic approach consisted of extensive re-education and information about the syndrome. Introduction of continuous delivery of insulin aspart was very cautious due to the risk of retinopathy. The follow-up CGM after 18 months showed 50% of measurements within the range (Figure 2(b)).

HbA1c decreased gradually to 7.4% within 2.5 years and was stable afterward. The liver size returned to normal after 6 months (11/14 cm; midclavicular/midhepatic line; Table 1). His height improved reaching 13.1% (-1 SD), weight was at 15% (appropriate for the height) after 2.5 years, while puberty reached stage 4. Hepatic enzymes and microalbuminuria improved. Fundus analysis was followed at 6-month intervals. There was no retinopathy on fundoscopy 2.5 years after the introduction of pump therapy.

Discussion

Mauriac syndrome is a rare disorder but was more common before long-acting insulins were introduced for the treatment of DM1 and before HbA1c was introduced as a marker of long-term glycemic control. Isolated patients with this syndrome are still being reported.^{3,7–10} The pathophysiology of this entity has not been elucidated. High index of suspicion for this syndrome should be maintained in a poorly controlled diabetic child with delayed growth. The mechanism of growth failure in this condition encompasses insufficient tissue energy (glucose) availability, decreased circulating IGF-1, and a relative growth-hormone-resistant state.¹¹ Circulating IGF-1 could be decreased because of decreased IGF-1 synthesis and secretion due to lack of the stimulatory effect of insulin and sex steroids or malnutrition. Our patient had low growth hormone (GH) and IGF-1 levels. Elevated levels of GH have occasionally been noted in poorly controlled DM1 with low IGF-1 indicating acquired GH insensitivity.¹¹

Hepatomegaly is a typical sign of Mauriac syndrome and appears in the majority of affected patients.¹² In the decompensation phase of the disease, liver glycogenesis can be found in response to poorly controlled diabetes; hepatomegaly in general occurs because of the deposition of glycogen in the hepatocytes, which is due to the facilitated glucose diffusion providing glycogen storage.^{12,13} It can be associated with a variable degree of liver enzymes derangement. Even when absent, the synthetic function of the liver can be affected, as determined by low albumin levels and an extended prothrombin time. Sometimes hepatic involvement is mild as it was in our patient. None of the autoimmune diseases known to be associated with Mauriac syndrome, such as Addison's disease, autoimmune gastritis, celiac disease, and hypothyroidism, were present in our patient.¹

Improvement of the metabolic control in children with Mauriac syndrome is mandatory and includes treatment with insulin analogues;⁸ however, if it is introduced too fast, retinopathy can be induced or existing retinopathy and/or nephropathy can be aggravated within months.^{5,6}

Our patient was treated with continuous insulin delivery. This approach has been used by Imtaz et al.¹⁴ in a patient with DM1 and glycogenic hepatopathy; however, no other features of Mauriac syndrome in this patient were mentioned, and no data about the ophthalmological finding were given. Continuous insulin delivery might be a good choice of treatment in patients

Table 1. Abnormal biochemical and other values in a patient with Mauriac syndrome.

Laboratory analysis	Result (normal values) at diagnosis	1 year after diagnosis	2.5 years after diagnosis
HbA1c	11.9% (4.5%–6.2%) 105 (24–43) mmol/mol ^a	9.2% 77.0	7.4% 57.4
C-peptide	0.1 (0.8–3.1) ng/dL	NA	NA
ALT	188 (9–72) U/L	65 U/L	49 U/L
AST	265 (15–59) U/L	50 U/L	45 U/L
GGT	74 (0–36) U/L	25 U/L	28 U/L
Total proteins	62 (64–83) g/L	69 g/L	72 g/L
Albumin	36 (40–49) g/L	42 g/L	43 g/L
Growth hormone peak value (L-dopa test)	1.85 (>10) ng/mL	NA	NA
IGF-I	25 (25–1600) ng/mL	70 ng/mL	NA
Testosterone	<20 (100–1200) ng/dL	120 ng/dL	218 ng/dL
Prothrombin time	33" (24")	Normal	NA
Microalbuminuria	150 (2.5–28) ng/mL	50 ng/mL	30 ng/mL (26 mg/g creatinine) ^b
Other analyses			
X ray (wrist)	Delayed maturation	NA	NA
CGMS	High variations	Less variable ^c	NA
Ultrasound of the liver (midclavicular/midhepatic line)	19/24 cm	11/14 cm	11/13 cm

NA: not applicable; ALT: alanine transaminase; AST: aspartate aminotransferase; CGMS: continuous glucose monitoring system; IGF-I: insulin-like growth factor-I; GGT: gamma-glutamyl transpeptidase.

^aMeasured by turbidimetric inhibition immunoassay; Siemens (Dade Behring) Dimension RxL Max (Glasgow), limits are given by the provider.

^bOnly at the last visit the measurement of microalbuminuria/creatinine was measured.

^cThe second CGMS was performed after 1.5 years at HbA1c = 8.4% (68.3 mmol/mol).

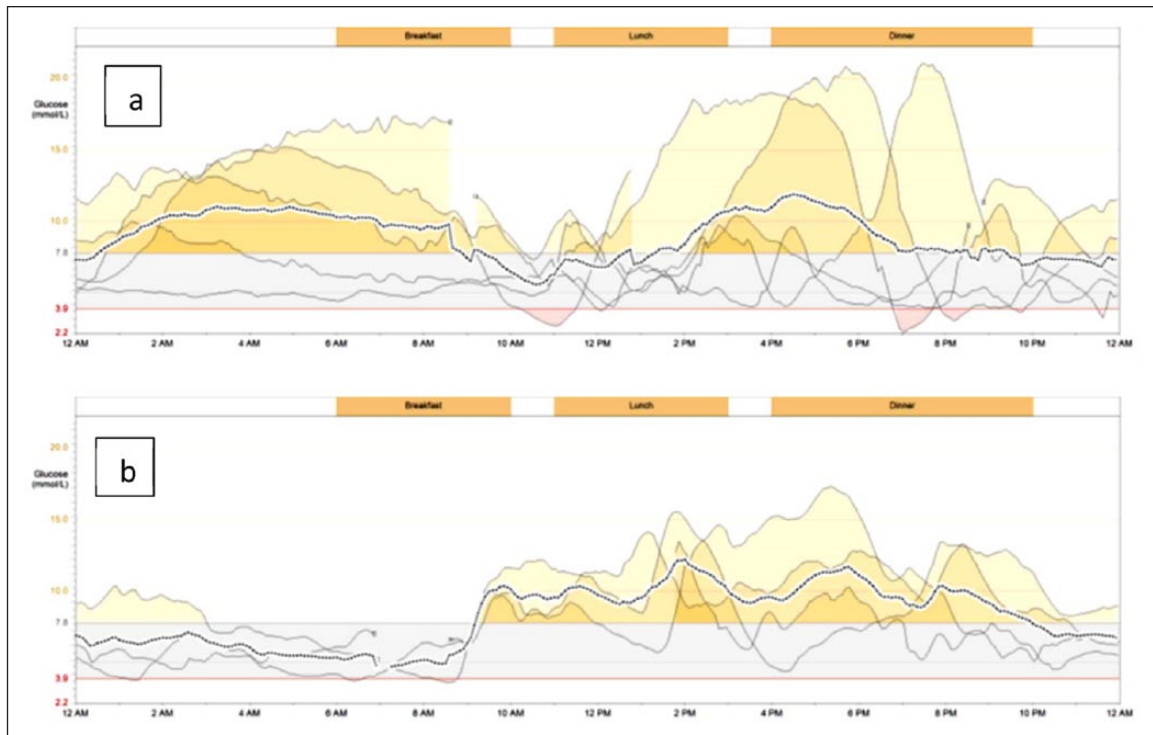


Figure 2. (a) CGMS at diagnosis with extremely large glycemic variations (HbA1c 11.9%–105 mmol/mol), several hypoglycemic events per day. (b) CGMS after 1.5 years showing less glycemic variations (HbA1c 8.4%–68.3 mmol/mol), good overnight control, higher daily values, and no hypoglycemia. Daily levels still need improvement.

with Mauriac syndrome due to the possibility of step-by-step improvement of the metabolic control and avoiding large variations of the glycemia. International experience with insulin pump therapy shows that the improvement of metabolic control is stepwise in the range of 0.5–1.0 for the HbA1c.¹⁵

Improvement of metabolic control usually abolishes the clinical signs of Mauriac syndrome. Features of Mauriac syndrome disappeared in our patient similarly as reported in the literature. In a large review of 18 patients (1971–2008), Kim et al.¹⁰ report that hepatomegaly and increased liver enzyme levels were the first to resume if the metabolic control was achieved. The acceleration of growth under improved metabolic control is variable and depends on the age and metabolic control. The final height depends on the age and initial growth deficiency.¹⁰

Conclusion

Patients with Mauriac syndrome are still detected despite the global improvement of metabolic control in children with diabetes. In a child with DM1 and stunted growth, other signs of the syndrome should be sought for, in order to achieve an earlier diagnosis of mild forms and timely insulin therapy adjustment. Applying continuous insulin delivery and continuous glucose measurements might be an appropriate approach to treat these patients in order to improve the clinical outcome and avoid complications. However, further investigation of this method in patients with Mauriac syndrome is warranted.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent from the mother and assent of the patient were obtained to present a case including the photographs. They are available upon request.

ORCID iD

Mirjana Kocova  <https://orcid.org/0000-0001-7097-3439>

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