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Insulin-Like Growth Factor (IGF-I) in Mauriac Syndrome or Diabetic Dwarfism

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Mauriac syndrome is characterized by the development of dwarfism, obesity and hepatomegaly in patients with insulin dependent diabetes mellitus (1). Growth retardation and hepatomegaly in diabetes mellitus should alert physicians over the insufficient management of diabetes mellitus and the related development of Mauriac syndrome. The cause of growth failure in Mauriac syndrome has remained obscure, although it is presumably related to the poor metabolic control of diabetes (2). Growth hormone deficiency has not been found in reported cases of Mauriac syndrome (3,4). The most important growth promoting effect of growth hormone is mediated by IGF-I (5). The determination of IGF-I and insulin-like growth factor binding protein 3 (IGF-3) had become a widely used tool in the diagnostic evaluation of growth disorders. Although IGF-I levels are commonly considered an indication of growth hormone (GH) secretion or action, its synthesis and secretion are regulated by a multi-factorial and complex mechanism. Nutrition, insulin, sex steroids, cortisol, and thyroxin have positive stimulatory effects on the release of IGF-I (6). We report on two cases of diabetes mellitus associated with Mauriac syndrome and limited joint mobility.

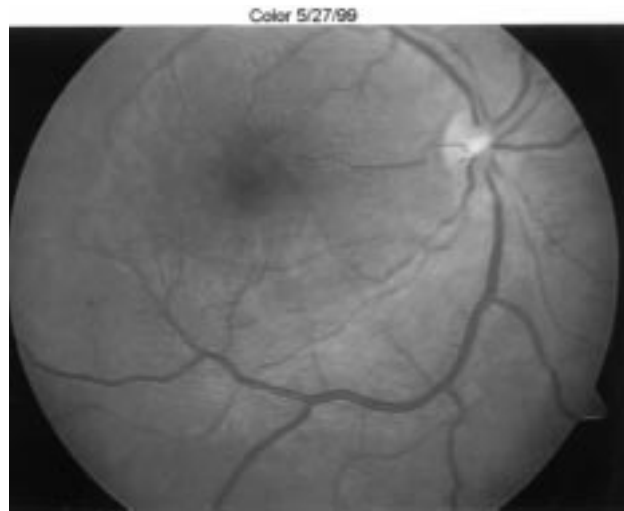
Case one

A 15-year-old girl with a 10-year history of type I diabetes mellitus was admitted for evaluation of short stature and hepatomegaly. The patient was administered an insulin mixture (Mixtard 30 HM[®], Novo Nordisk) of 0.4-unit/kg of body weight per day in two doses for a 4-

year period. She claimed that she had hyperglycemia and glycosuria during the last 2 years. The patient was hospitalized for regulation of diabetes mellitus. Her weight was 42.5 kg (5th percentile for age and gender) and height was 147 cm (< 3rd percentile for age and gender, -2.5 SDS). Bone age was 12^{6/12} years. Physical examination revealed that she had a thick and cold skin, protuberant abdomen, hepatomegaly, stage III puberty development according to the Tanner grading system, and limited-joint mobility (Figure 1A). The findings of the physical examination were in accordance with the diagnosis of Mauriac syndrome. Laboratory analyses were as follows: hemoglobin A1c was 18.5% (normal 4.2 to 6.4%); hemoglobin 11 g/dl; total protein 6.6 g/dl; albumin 4.4 g/dl; triglycerides 116 mg/dl (normal 35-138 mg/dl); cholesterol 185 mg/dl (normal 109-190 mg/dl); aspartate aminotransferase 21 U/L (normal 5-45 U/L); alanin aminotrasferase 36 U/L (normal 5-45 U/L); IGF-I 78 ng/ml (normal range for age and gender 193 to 691 ng/ml); FSH 2.3 mIU/ml; LH 1.7 mIU/ml; E2 23.9 pg/ml; and urinary albumin excretion rate 160 µg/min (normal < 20 µg/min). We did not have the opportunity to measure IGFBP-3. Blood glucose values fluctuated between 190 and 320 mg/dl. The results of thyroid hormones and growth hormone stimulation tests were within normal ranges. The retinal angiofluorescein revealed macular edema and increased diffuse hard exudates and extensive hemorrhages (Figures 1B and C). The dietary calorie intake was increased from 1500 kcal to 2500 kcal and insulin dose was increased from 24 units/day to 52 units/day. Intensive insulin therapy was recommended. Nine months after her therapy revision



A



B



C

Figures 1A-C. Photograph A showing limited joint immobility in patient 1; B-C, the retinal angiofluorescein showing macular edema, increased diffuse hard exudates, and extensive hemorrhages in patient 1.

she grew 2 cm taller, and hepatomegaly disappeared. We had no information on her growth rate for preceding years. Nine months later, IGF-I was 345 ng/ml.

Case two

An eleven-year-old boy was admitted because of diabetic ketoacidosis. He had been followed up for a six year history of type 1 diabetes mellitus and treated by a

two-dose insulin regimen. He had been taking a total mixture insulin (Mixtard HM[®] 20, Novo Nordisk) of 0.5 units /kg/day, and was on a 1500 kcal diet for three years. His weight was 24 kg (< 3rd percentile for age and gender) and his height was 122 cm (1st percentile for age and gender, -3SDS). Bone age was 8^{6/12} years. Physical examination revealed that he was very small with a protuberant abdomen and hepatomegaly. Puberty was at stage I according to testis size. He had limited joint

mobility. The findings of the physical examination were in accordance with the diagnosis of Mauriac syndrome. Laboratory analyses were as follows: hemoglobinA1c, 21% (normal 4.2 to 6.4); hemoglobin 10.4 g/dl; blood glucose 780 mg/dl; blood urea nitrogen (BUN) 89 mg/dl; creatinine 1.1 mg/dl; Na 128 mEq/L; K, 5.8 mEq/L; blood ketones (+++) positive in $1/2$ dilution of serum; urine ketones positive; triglycerides 83 mg/dl (normal 35-138 mg/dl); cholesterol 170 mg/dl (normal 109-190 mg/dl); aspartate aminotransferase 12 U/L (normal 5-45 U/L); alanin aminotrasferase 29 U/L (normal 5-45 U/L); and IGF-I 34 ng/mL (normal for age 85 to 339 ng/ml). We did not have the opportunity to measure of IGFBP-3. Urinary albumin excretion rate was 98 μ g/min (normal < 20 μ g/min). Ophthalmologic examination was normal. The ketoacidosis of patient 2 was successfully treated by short-acting insulin infusion and he has followed up intensive insulin regimen. Renal function tests were in normal ranges, except for microalbuminuria. Total daily insulin dose was increased from 12 units to 20 units. Blood glucose was analyzed three times a day. He was discharged and followed the same insulin regimen of patient one. Nine months later physical examination revealed that he weighed 27 kg, height was 126 cm, hepatomegaly had disappeared, and microalbuminuria had persisted. Blood glucose values over the nine months were between 60 and 190 mg/dl, HbA1c was 9.8%, and microalbuminuria was between 98 and 172 mg/min. Nine months later, IGF-I was 126 ng/ml.

The cause of growth failure in Mauriac syndrome remains obscure, although it is presumably related to poor metabolic control of diabetes (2). Mauriac syndrome is associated with hepatomegaly and diabetic dwarfism. Growth hormone stimulation tests in Mauriac syndrome were in normal ranges in a number of reports (3,4,7). It was also suggested that decreased growth velocity must be related to underinsulinization over a long period and poor metabolic control of diabetes mellitus (8,9). Our two patients had received low insulin doses and low calorie diets for a long time. The combination of underinsulinization and low calorie diets caused Mauriac syndrome. Extremely high levels of HbA1c, hyperglycemia and retinal findings in case 1, and diabetic ketoacidosis in patient 2 supported insufficient insulin therapy.

Patient heights were in accordance with the diagnosis of dwarfism. Low levels IGF-I can explain the etiology of

dwarfism. The IGF-I levels of the patients were found under the first percentile of the age and gender-dependent normal range (6). To our knowledge, this is the second report in the English literature that demonstrates low-level IGF-I associated with diabetic dwarfism or Mauriac syndrome (3). Low level IGF-I secretion was explained by low-dose insulin over a long time, and delayed puberty. Insulin and sex steroids have stimulatory effects on the synthesis and secretion of IGF-I (6). However patient 1 had stage III puberty, and the IGF-I level was below the normal range. This finding was supported by the fact that the control of IGF-I synthesis and secretion was multifactorial. Cases of Mauriac syndrome show that normal insulinization and normal caloric intake are factors that affect the synthesis and secretion of IGF-I. This hypothesis was supported by the fact that the IGF-I levels of our patients were in normal ranges after the normalization of caloric and insulin intake. Chronic nutritional deprivations suppress the secretion of IGF-I (10,11). The IGF-I levels in our patients were normalized by adequate insulin administration and caloric intake. Similar changes to the growth rate did not occur after the regulation of insulin therapy and caloric intake. However, patient 2 exhibited a normal growth rate, though patient 1 had an inadequate growth rate despite normal IGF-I levels. There is only one prospective study on the effect of IGF-I in Mauriac syndrome by Mauras et al. (12). Normal hypothalamic-pituitary function, normal growth hormone binding protein, IGF-I generation, and insulin-like growth hormone binding proteins in two patients with Mauriac syndrome were compared with normally growing diabetic children. They found an inadequate response to exogenous growth hormone therapy and concluded that a growth hormone resistant state existed either secondary to impaired bioactivity of IGF-I, or as a defect at or distal to the IGF-I receptor. The growth pattern of patient 1 can be explained by a growth hormone resistant state. Patient 2 showed the same growth pattern compared with his peers after IGF-I normalization by normal caloric intake and adequate insulinization. There is very limited research associated with Mauriac syndrome and IGF-I and IGF-BPs in the literature and we were unable to compare our results.

Limited joint mobility is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and neuropathy, which may appear before 18 years of age (13,14).

In conclusion, our data show that the growth pattern in Mauriac syndrome is affected by underinsulinization and inadequate caloric intake, but they are not the sole factors in diabetic dwarfism. There is a need for additional prospective studies to explain the exact mechanism of diabetic dwarfism in Mauriac syndrome.

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