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CASE REPORT

Nephrocalcinosis in a 13-year-old girl with type 1 diabetes mellitus complicated by Mauriac syndrome

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Mauriac syndrome is a rare complication of poorly-controlled type 1 diabetes mellitus (T1DM) characterised by hepatomegaly, short stature, and pubertal delay. We report the case of a 13-year-old girl with T1DM who presented to our hospital with hyperglycaemia and hepatomegaly, and was also found to have bilateral medullary nephrocalcinosis. It is hypothesised that chronic hyperglycaemia resulting from long-term insulin under-dosage led to chronic acidosis which caused hypercalciuria and consequently, nephrocalcinosis. Poor glycaemic control, Mauriac syndrome and nephrocalcinosis, may be associated with socio-economic difficulties. Both medical optimisation and psychosocial support should be provided to reach optimal glycaemic targets, reverse the features of Mauriac syndrome, and prevent worsening of nephrocalcinosis that could potentially lead to chronic renal impairment.

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Introduction

Pierre Mauriac first described a syndrome of growth failure, delayed puberty, and hepatomegaly in children with poorly controlled type 1 diabetes mellitus (T1DM) in 1930.[1] With improved diabetes care, Mauriac syndrome has become less prevalent, but may still be encountered from time to time. The exact underlying pathogenesis remains unclear, although a genetic enzyme defect of glycogen metabolism has been proposed.[2] Conditions predisposing to Mauriac syndrome include insufficient insulin (be it through poor adherence or sub-optimal insulin regimen) and a diet with severe caloric restriction.[3] Other reported associated features include raised serum transaminases, dyslipidaemia, and Cushingoid features. [4-5]

We report the case of a 13-year-old girl diagnosed with Mauriac syndrome and having the additional feature of nephrocalcinosis, which to the best of our knowledge has not been reported before.

Case Presentation

A 13-year-old, North African refugee girl, rescued at sea whilst crossing the Mediterranean in a ramshackle boat in search of asylum in Europe, presented to our hospital with hyperglycaemia and dehydration. The criteria for diabetic ketoacidosis were not fulfilled, and she was initially managed with subcutaneous insulin and intravenous rehydration fluids. She had been diagnosed with T1DM at the age of 5 years in her home country. Details of her initial presentation at diagnosis and her clinical course over the years were not available, but glycaemic control had been sub-optimal due to a combination of limited access to insulin and poor adherence to treatment. Furthermore, during her sea-crossing she had been rationing her dwindling supply of insulin and food and, a few hours before her rescue, had even lost her last remaining insulin cartridge in the sea.

On examination, she was noted to have soft, tender hepatomegaly (10 cm below right costal margin) and to be prepubertal (Tanner stage 1). Significant lipohypertrophy was noted at insulin injection sites below the umbilicus. There was no palpable splenomegaly, free fluid in the abdomen, or clinical signs of chronic liver disease. Auxological measurements revealed a height of 146.9 cm (-1.3 SDS), weight of 37 kg (-1.24 SDS), and body mass index of 17.1kg/m^2.

Initial laboratory investigations showed a glycosylated haemoglobin of 11.70% (104 mmol/mol), an elevated serum alanine transaminase (ALT) of 104 units/L (reference range: 5-33units/L) and an elevated gamma glutamyl transferase (GGT) of 210 units/L (reference range: 5-36 units/L), but normal serum alkaline phosphatase, bilirubin and albumin, as well as normal serum concentrations of urea, creatinine, sodium, potassium, chloride, normal full blood cell, and venous pH and bicarbonate.

Further investigations for hepatomegaly were taken. A viral screen for hepatitis B, hepatitis C, Epstein Barr virus, cytomegalovirus, rubella, and herpes simplex was negative. Toxoplasma antibodies were negative. Iron studies and a lipid profile were also normal. An ultrasound of the abdomen revealed hepatomegaly (measuring 4 finger breaths below the costal margin and extending at least 3 cm below the lower pole of the right kidney), with steatosis. There was no intra- or extra-hepatic biliary duct dilatation, and normal hepatopetal flow was seen within the portal vein. The spleen was slightly enlarged for patient's age (measuring 12cm) but demonstrated normal echotexture. Hyperechogenicity of both renal medullae suggestive of bilateral medullary

nephrocalcinosis was noted (Figure 1). There was no nephrolithiasis or hydronephrosis.

Serologic testing for coeliac disease and thyroid function tests, performed routinely as screening for auto-immune conditions associated with T1DM, and also because of the patient's short stature, were all normal.

At this point, Mauriac syndrome was suspected based on the findings of hepatomegaly, short stature, pubertal delay, and elevated serum ALT, in a patient with poorly-controlled T1DM.

Further investigations were performed to elucidate the cause of the nephrocalcinosis seen on ultrasound. Repeated measurements of serum calcium showed concentrations consistently within the reference range (corrected calcium 2.17-2.36mmol/L; reference range: 2.05-2.60mmol/L). Serum phosphate, magnesium and bicarbonate were also normal. Serum parathyroid hormone concentrations were within the reference range.

To assess for hypercalciuria, a random spot urine for calcium, as well as a 24-hour urine collection, were performed. The spot urine calcium/creatinine ratio was borderline high at 0.55 (mmol/mmol; normal < 0.56). However, the 24-hour urine collection for oxalate, calcium, phosphate, citrate and creatinine showed results that were within the respective reference ranges. The urinary calcium excretion rate was normal at 3.02mg/kg/day (normal: < 4mg/kg/day), equivalent to 0.07mmol/kg/day (upper limit of normal: 0.1mmol/kg/day). Urine albumin/creatinine ratio was normal at 16.44mg/g (reference range: 1-20mg/g), and there was no microalbuminuria (result: 5.90mg/L; reference range: 3-20mg/L). Urine pH was also normal.

The insulin regimen was adjusted and insulin doses were titrated to improve glycaemic control. Diabetes education was offered to both the child and her parent. A balanced, healthy diet was introduced and encouraged. An exercise programme was also set up whilst the patient was hospitalised. In view of the poor socio-economic background and the dramatic entry into the country, social work input was also sought and it was ensured that the child would be discharged to a safe environment, with proper access to medication, food and regular medical review.

As glycaemic control gradually improved, the hepatomegaly and associated tenderness also regressed. Two months after presentation, the serum concentrations of GGT and ALT had normalised. Glycosylated haemoglobin had also improved to 9.2% (77 mmol/mol). There was also a weight gain of 12.5 kg (+0.35 SDS; Figure 2) and the initiation of bilateral breast development (Tanner stage 2). This clinical improvement that occurred once glycaemic control was restored, strengthened our initial diagnosis of Mauriac syndrome.[4-5]

A repeat ultrasound abdomen was planned for six months' time from presentation, but the patient relocated to another country after five months.

Figure 1 Ultrasound images of both kidneys showing hyperechogenicity of the renal medullae indicative of medullary nephrocalcinosis

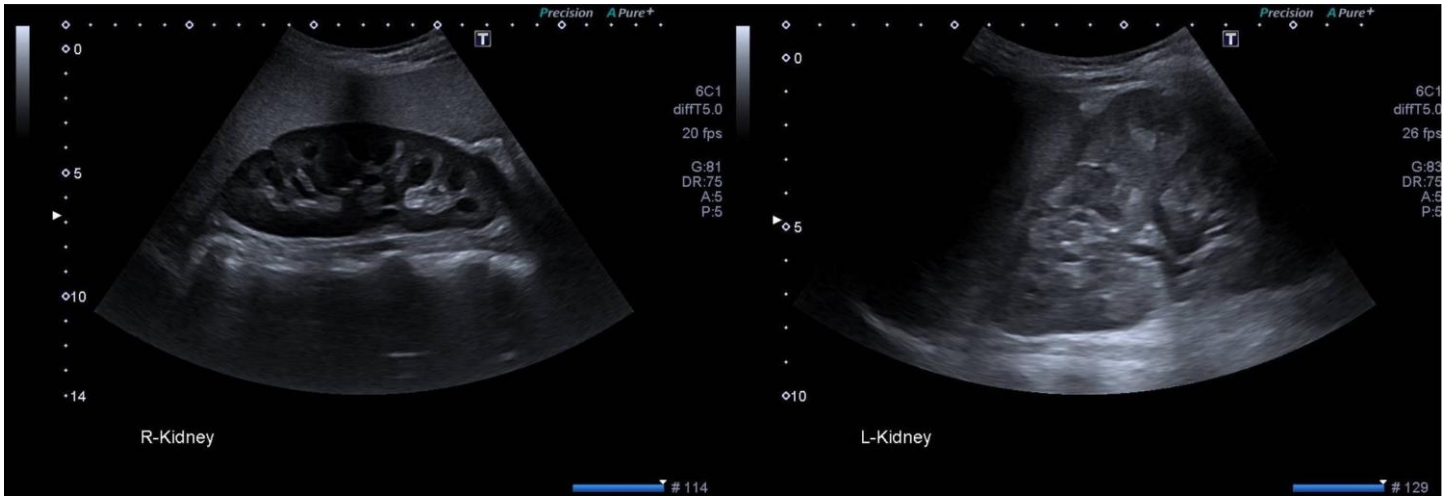
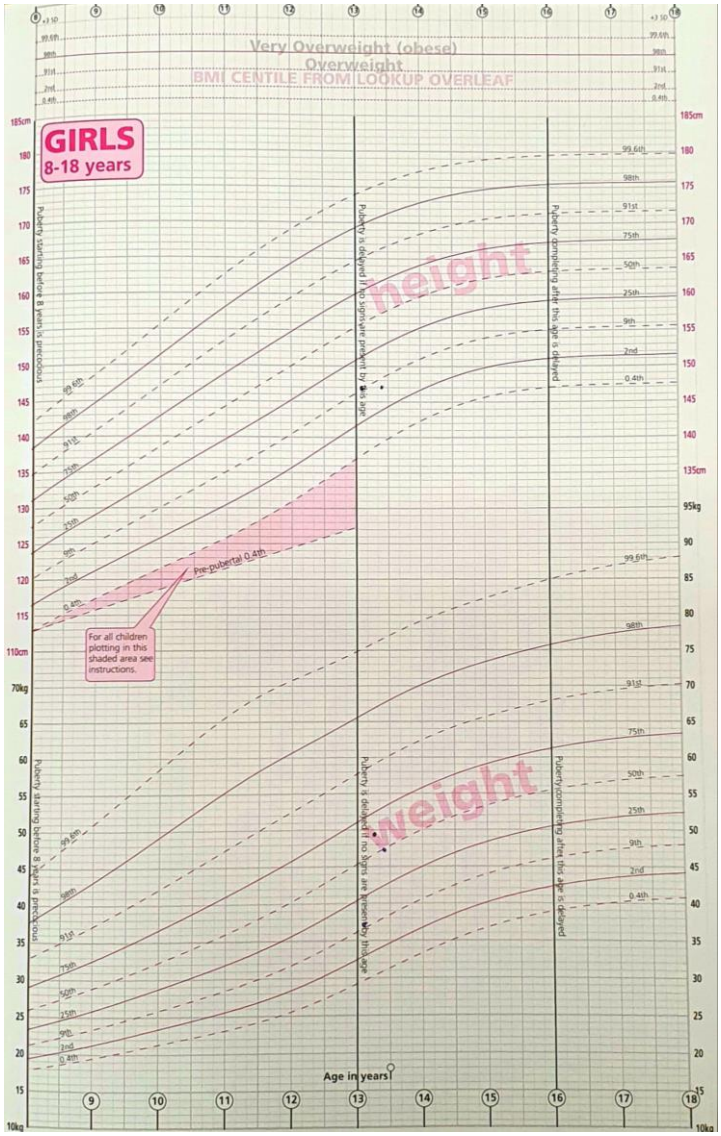


Figure 2 Patient's growth chart



Discussion

This case demonstrates the main characteristics of Mauriac syndrome. Nephrocalcinosis, however, is not a recognised feature of Mauriac syndrome. Investigations to determine a cause for the nephrocalcinosis were within normal limits, and there was no relevant family history that could point towards renal tubular acidosis or a tubulopathy, as well as no evidence of bone disease. It was thus deduced that the nephrocalcinosis was secondary to chronic uncontrolled T1DM.

It is hypothesised that long-standing hyperglycaemia leads to chronic acidosis which can cause hypercalciuria (and subsequent nephrocalcinosis) in various ways. Chronic acidosis results in increased osteoclast action and decreased osteoblast action. The net effect is increased calcium efflux from bone leading to hypercalciuria. Increased hydrogen ions in the circulation displace calcium bound to albumin, leading to increased serum ionised calcium concentrations and, thus, also to hypercalciuria. Acidosis also alters the renal absorptive capacity of calcium by direct inhibition of calcium transport in the nephron.[6]

Whether nephrocalcinosis can be considered a feature of Mauriac syndrome or whether it is purely a complication of long-standing uncontrolled T1DM is not possible to determine from this single case. Renal impairment due to microangiopathy has long been associated with poor glycaemic control of diabetes, but nephrocalcinosis itself has only rarely been reported. Also, unlike the case described by Kodama et al.[7], renal function was normal in our patient, despite the clearly evident nephrocalcinosis on ultrasound.

Nephrocalcinosis can damage the distal nephron resulting in distal renal tubular acidosis or nephrogenic diabetes insipidus. Progressive renal impairment is usually rare unless obstructive nephrolithiasis supervenes. Once present, the nephrocalcinosis is unlikely to be reversed (despite normoglycaemia and resolved acidosis and hypercalciuria), and management is aimed at preventing deterioration.[8] This can be achieved by preventing further hypercalciuria from chronic acidosis due to poor glycaemic control.

The clinical features and biochemical derangements associated with Mauriac syndrome regress with optimised glycaemic control, but great care has to be taken as too-rapid improvements can lead to deterioration of retinopathy and nephropathy.[4]

With poor glycaemic control, and indeed in most reported cases of Mauriac syndrome, there are often associated socio-economic difficulties.[4, 5, 9, 10] Both medical optimisation and psychosocial support have to be provided to improve glycaemic control, and thus reverse the features of Mauriac syndrome, ensuring optimal growth and development, and prevention of long-term diabetes complications, as well as, in our case, worsening nephrocalcinosis. Recognition of Mauriac syndrome in T1DM is also important to avoid misdiagnosis[7] and thus invasive investigations (such as a liver biopsy).

A final learning point exemplified by this case is to recognise (and thus manage) the difficulties and health inequities of migrants at various points of their journey, especially those suffering from chronic disease requiring treatment, such as T1DM.

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