Insulin Dependent Diabetes Mellitus Accompanied by Nephrocalcinosis and Renal Failure

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Abstract. Renal failure was found in a five-year-old patient who had been treated with insulin since he was diagnosed as having insulin dependent diabetes mellitus (IDDM) at 3 years of age. Laboratory data showed that his renal failure was caused by a renal tubular dysfunction. The autopsy findings of his pancreas were compatible with those of IDDM. The kidneys were atrophied with an innumerable number of crystals in the proximal tubuli. Staining by Kossa indicated that the crystals contained calcium salt. The calcium content of his kidneys was significantly higher than that of control. The nephrocalcinosis seems to be caused by hypercalciuria associated with IDDM.

Key words: Insulin dependent diabetes mellitus, Nephrocalcinosis, Renal failure.

INSULIN dependent diabetes mellitus (IDDM) is often associated with microangiopathy of the kidney, which cause renal failure. However, nephrocalcinosis with renal failure has hitherto not been reported in IDDM. We describe here a five-year-old patient with IDDM and nephrocalcinosis that resulted in renal failure.

Case Report

The patient was a five year and four month old Japanese boy who had been treated with insulin since he was diagnosed as having IDDM at 3 years of age. When his IDDM was first diagnosed, the levels of his blood urea N (BUN) and serum creatinine were normal. No members of his immediate family and none of his other relatives had diabetes mellitus or any kind of renal disease. During the follow-up period in the out-patient clinic, he had no pyelonephritis, proteinuria, pyuria, hematuria, oliguria, hypotension or diabetic coma. His IDDM seemed to be out of control, because his serum glycohemoglobin level was between 8.8 and 18.6% (13.1±3.1, n=8, Mean±SD; normal, 4–8%). He had appetite loss, general fatigue and sometimes vomiting for four months before admission. At admission, the urine output was reasonably good. No edema or dehydration were observed. His height and weight were normal. No hepatosplenomegaly was found. The levels of BUN and serum creatinine were normal. No members of his immediate family and none of his other relatives had diabetes mellitus or any kind of renal disease.

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IgM, GOT, GPT, alkaline phosphatase, uric acid, cholesterol, triglyceride and complements (C3 and C4) were normal. The serum levels of Ca and P were 10.2 and 4.6 mg/dl, respectively (normal: Ca: 8.4–10.4 mg/dl, P: 2.0–5.0 mg/dl). During his stay in the hospital, the serum levels of Ca, P and Mg were always normal; neither metabolic acidosis nor alkalosis was observed; and his blood pressure was 98/72 mmHg. His fundus had no retinopathy of diabetes mellitus. His renal function tests were as follows: The urine volume was between 500–1500 ml/day. Urinary Na excretion was 87 mEq/l and FENa was 1.06%. The levels of his creatinine clearance and PSP test were decreased to 18 ml/min and 4% (15 min), respectively. The urinary levels of β2-microglobulin and N-acetyl β-glucosaminidase were increased to 730 μg/l (normal <250) and 24.6 U/g creatinine (normal <4), respectively. Renal concentrate function was disturbed with maximum urine specific gravity at 1.015. His urine pH was 5.0–7.5. No proteinuria, hematuria or pyuria was found. Urinary amino acids were within the normal ranges. His kidney and pelvis were not detected by intravenous urography. No calcification in his kidney was found by roentgenograms or echograms. He was treated with a low protein diet, the administration of insulin and intravenous infusion of essential amino acids. However, the BUN decreased to only 57 mg/dl. He died from a hypoglycemic attack at the age of 5 years and 8 months.

Pathological findings

The pancreas (Dept. Pathol. A-1940) showed severe atrophy and weighed only 22.8g. Histologically, Langerhans islets, including vestigial ones, were decreased in number, although there was no hyalinization at all. They were markedly irregular in shape and size, depicting papillary, adenomatous and cribriform structures. No B-cells were demonstrated by the immunohistochemical examinations. A-and D-cells were positively stained by the glucagon- and somatostatin staining
method, respectively. These findings in the pancreas were compatible with those of IDDM. The both kidneys were extremely atrophied and their weight was only 35 g (control weight, left 52.7 g, right 51.0 g). There were an innumerable number of yellowish and point-shaped crystals, mainly in the cortex, with a lesser number in the medulla. These crystals were found in the proximal convoluted tubules, and the epithelium was occasionally replaced with the crystals (Fig. 1). A small number of these crystals were distributed in the interstitium. It was presumed that the crystals contained no calcium oxalate, but they did contain calcium phosphate. They were stained black by the calcium salt stain of Kossa (Fig. 2), but no birefringence was demonstrated by a polarizing microscope. We could not see any glomeruli with diabetic nodular sclerosis or any arteries with diabetic vascular hyalinosis. There was slight congestion of the liver, but there were no cysts, calcification or inclusion bodies. There was no hyperplasia of the parathyroid.

**Calcium content of the kidney**

A part of postmortem kidneys from the patient and control individuals was dried at 105°C overnight and then weighed. After the tissue was wet-digested with 50% HNO₃ by heating, the clear residual liquid was adjusted to 2M HNO₃ by addition of double distilled water. The calcium content was analyzed with an atomic absorption spectrophotometer. The calcium content in his kidneys was 40 mg/g dry weight, which was significantly higher than that of controls (normal 0.38±0.18, n=4, Mean±SD).

**Discussion**

This patient developed chronic renal failure during the course of the treatment of IDDM. His laboratory data, such as urine volume and FENa, demonstrated intrinsic renal failure. Renal function tests showed renal tubular dysfunction. Postmortem examination of the kidneys revealed degenerative changes in tubular cells accompanied by marked nephrocalcinosis. These results suggest that renal tubular damage caused the renal failure. Nephrocalcinosis was the most characteristic finding in the postmortem examination.

Nephrocalcinosis without hypercalcemia is
known in many diseases [1–3]. For example, it is observed in hereditary renal tubular acidosis, Fanconi syndrome accompanied by cystinosis, Wilson’s disease, glycosegenosis or galactosemia [4], persistent alkalosis, hyperoxaluria [5], normocalcemic hyperparathyroidism, medullary sponge kidney, congenital magnesium-losing kidney [6], recurrent pyelonephritis, familial hypercalciuria and idiopathic hypercalciuria. However, the renal disturbance in this case was apparently not caused by any of these diseases for the following reasons: no renal diseases were found among the family members. In addition, the urine pH of the patient sometimes decreased to maintain the normal pH of the blood. These data denied hereditary renal tubular acidosis and familial hypercalciuria in the patient. Fanconi syndrome and persistent alkalosis were denied by his clinical course and laboratory data showing no alkalosis in the blood; and the serum K level was within the normal range. He did not suffer from pyelonephritis. The autopsy findings on his kidney showed neither medullary sponge kidney nor hyperoxaluria.

Hypercalciuria has been observed in some patients with IDDM [7, 8]. Malone et al. [9] warned that many children with IDDM are at risk for renal damage or renal calculus formation due to hypercalciuria. Since the nephrocalcinosis in this patient was not found until the autopsy, PTH and vit. D metabolites in the serum and urinary calcium excretion were not examined. However, the renal calcium deposits in this case were most severe in the tubular cells, and the renal failure was caused by renal tubular dysfunction. These observations suggest that this patient had hypercalciuria. Therefore, the possible cause of the nephrocalcinosis with renal failure in this patient was hypercalciuria associated with IDDM, though other causes could not be denied. The experience with this patient tells us that determination of the urinary calcium concentration should be added to periodic urinalyses in patients with IDDM.

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References