

Case Report

Type 1 glycogen storage disease and recurrent calcium nephrolithiasis

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Introduction

Type 1 glycogen storage disease (type 1-GSD) is a rare inherited metabolic disease characterized by a glucose-6 phosphatase deficiency [1], which is frequently complicated by renal stone disease. Urate stones have been considered the most common stone type, although calcium oxalate stones have also been described.

We report a case of a patient with type 1-GSD and recurrent calcium stone disease, with multiple metabolic alterations, including hypercalciuria, hypocitraturia and hyperoxaluria. Severe hyperlipidaemia, hyperuricaemia and osteoporosis were also present. The potential lithogenic metabolic alterations observed, as induced by this hereditary disease, and possible implications for its medical management are discussed.

Case

A 15-year-old male patient was referred to the out-patient renal stone clinic of the Santa Maria Hospital for metabolic evaluation because of recurrent renal stone disease. The patient had a type 1-GSD diagnosis since the age of 7 months, with several hospital admissions because of uncompensated lactic acidosis and/or hypoglycaemic episodes. Severe hyperlipidaemia (total cholesterol >900 mg/dl) and hyperuricaemia were also present. Gouty episodes were not described. He was being treated with a diet which included frequent meals during the day, a low lactose-formula milk and 80 g of uncooked corn starch every 6 h. He was also taking allopurinol in a dose of 200 mg/day.

Three months before observation he had a first renal colic. In a second episode, 2 weeks later, a renal ultrasound revealed a stone in the left proximal ureter and left kidney obstruction; this stone was visible on the

plain abdominal radiograph. A catheter was placed in the left ureter and the patient was submitted to extracorporeal shock wave lithotripsy, with successful destruction of the calculus.

Physical examination revealed a short stature and slightly obese patient, with 146 cm height, 43.5 kg weight, with a round 'doll face'. Blood pressure was 110/80 mmHg. The abdomen was slightly enlarged and a smooth liver border was palpable 2–3 cm below the costal margin. No oedema was present. A renal ultrasound performed at this time revealed that both kidneys were normal sized, and that multiple small stones were present in both kidneys; on the plain radiograph a small stone was visible on the left kidney, of approximately 0.5 cm diameter.

For the purpose of metabolic evaluation allopurinol was stopped but no other modification was done. Blood and 24-h urine were collected in 2 consecutive days. In blood concentrations of creatinine, calcium, phosphorus, uric acid, alkaline phosphatase, sodium, potassium, chloride, intact PTH (iPTH) and calcitriol were measured; 24-h urine samples were analysed for volume and concentrations of creatinine, urea, calcium, phosphorus, uric acid, oxalate, citrate, magnesium, sodium, potassium, chloride and pH. A fresh urine sample was collected for urine culture, presence of crystalluria and pH. To exclude metabolic acidosis, a venous pH and bicarbonate was also measured. Metabolic evaluation was done 12 weeks after the last colic episode.

Laboratory results for blood creatinine, calcium, phosphorus, uric acid, sodium, potassium, chloride, alkaline phosphatase and calcitriol were normal; iPTH was 8 pg/ml (normal range: 12–72). A venous pH was 7.38 and bicarbonate was 27.2 mmol/l. Creatinine clearance was 80.5 ml/min. Urine volume was 2390 ml/day. There was hypercalciuria (321 and 351 mg/day; normal value ≤ 4 mg/kg/day, or ≤ 175 mg/day for this patient), hyperoxaluria (63.9 mg/day, on both days; normal value ≤ 45 mg/day), marked hypocitraturia (123 and 99.9 mg/day; normal value ≥ 320 mg/day). Urinary sodium (444 and 364 mmol/day) and chloride (275 and 325 mmol/day) were high, but potassium, magnesium, uric acid and phosphate were within normal limits; average urine pH was 5.0. Abundant calcium oxalate crystals were present in the fresh urine sample.

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Using a formula described by Mitch and Walser [2] based on urea excretion, an estimation of daily protein consumption was 1.1 g/kg/day. Using the formulas described by Tiselius [3] the activity product for calcium oxalate (AP(CaOx)) was 3.20 and the activity product for uric acid (AP(UA)) was 4.33E-07. A dual X-ray absorptiometry of the lumbar spine revealed a severe osteoporosis (BMD = 0.612 g/cm²; T-score -4.4). No renal stone was available for analysis, but a diagnosis of recurrent calcium stone disease secondary to type 1-GSD, with hypercalciuria, hyperoxaluria and hypocitraturia was made. Treatment was started with potassium citrate 30 mEq/day, allopurinol 100 mg/day and a combination of hydrochlorothiazide 25 mg/day with amiloride 2.5 mg/day. A low-sodium, low-oxalate and high-fluid diet was prescribed. To reduce further oxalate absorption from the gut, 500 mg calcium carbonate supplements were added to the three main meals.

Four weeks after starting therapy urinary volume was 2510 ml/day, oxalate 35 mg/day, sodium 90 mmol/day, chloride 228 mmol/day and urine pH 7.06; however, serum calcium (11.4 mg/dl) and serum uric acid (8.5 mg/dl) were above normal limits. Urinary calcium rose to 369 mg/day, uric acid rose to 1.15 g/day and urinary citrate remained low (119 mg/day). At that time a small number of calcium phosphate crystals was present in a fresh urine specimen. AP(CaOx) was reduced to 1.44 and AP(UA) to 3.09E-07. Calcium carbonate supplements were reduced to 250 mg at lunch and dinner only, and potassium citrate was elevated to 60 mEq/day with meals. Thiazide and allopurinol were maintained.

Two months later, serum calcium was within normal limits, urinary calcium was reduced to 117 mg/day, urinary citrate rose to 211 mg/day, and urinary sodium, potassium, chloride and magnesium were within normal limits. Urine volume was 2730 ml/day and pH 7.41. However, a disproportionate rise in urinary oxalate to 102 mg/day was observed and the levels of uric acid remained high, both in serum (8.2 mg/dl) and in urine (1.09 g/day). No crystals were present in the fresh urine sample. At this time the AP(CaOx) was 1.33, AP(UA) 1.32E-07 and no new stones were formed. Although blood levels of total cholesterol (344 mg/dl) and triglycerides (748 mg/dl) also remained very high, no rise was observed compared with pre-treatment levels. Allopurinol was increased to 200 mg/day and calcium carbonate supplements with meals were increased to 250 mg three times a day, given with main meals. The patient was advised to reduce further oxalate-rich foods and to maintain a high fluid intake, in order to keep a urine volume > 2 l/day.

Discussion

Type 1-GSD, also known as von Gierke's disease, is an inborn error of metabolism characterized by a glucose-6 phosphatase deficiency. As a result of the

incapacity to dephosphorylate glucose-6-phosphate, glucose production from glycogenolysis and gluconeogenesis is impaired and severe hypoglycaemia episodes can result [1]. Several renal complications have been reported in type 1-GSD, including nephrolithiasis, focal and segmental glomerulosclerosis and, less frequently, renal amyloidosis and Fanconi syndrome [4]. The cause for some of these complications is not well understood, but some authors admit they can be secondary to a defect of the tubular glucose-6-phosphatase, and adequate dietary measures aimed to correct hypoglycaemia could improve proximal tubular function [4]. Nephrolithiasis is the most frequently described complication. Part of the glucose-6-phosphate excess is metabolized by pentose phosphate shunt, leading to hyperuricaemia [1]. For this reason urate kidney stones have been considered a major cause in nephrolithiasis in the past, although calcium stones were also described. Unfortunately, in this case no stone was available for analysis and the exact stone composition was not known. This would be important because of the frequency that urate stones are produced in this disease. Based on the radiological aspect and the presence of calcium oxalate crystalluria, calcium stone disease was assumed. Factors contributing to this condition include hypercalciuria and hypocitraturia [5]. Low urinary citrate excretion is a well-established cause of nephrolithiasis [6] and changes in the acid-base status are the major determinant of citrate excretion. Citrate excretion is known to be reduced in acidosis, both by increasing citrate uptake by the proximal tubular cell in intracellular acidosis [7], and by a direct influence in the proximal tubular transport of citrate by the brush border membrane in response to a low luminal pH [8]. Chronic lactic acidemia is one of the main features of type 1-GSD. It results from overproduction of lactic acid as a consequence of deficient glucose production. In this case, chronic acidemia could explain hypocitraturia. As chronic acidosis has been considered a major cause of osteoporosis seen in these patients [1], its association with hypercalciuria could explain the severity of the osteoporosis.

Hypercalciuria and nephrocalcinosis have already been reported in type 1-GSD, and its pathogenesis could involve an incomplete form of distal tubular acidosis [5]. In the present case, an acidification test was omitted because the patient had a past history of severe lactic acidosis. Another possible mechanism to explain hypercalciuria in this patient is the very high sodium excretion observed at basal evaluation. The fact that the hypercalciuria persisted on a low-sodium diet cannot be interpreted because calcium supplements were already being administered in order to reduce oxalate absorption.

To our knowledge, hyperoxaluria has not been described in type 1-GSD. In this case it is impossible to say if it was merely of dietetic origin or if it was secondary to the underlying enzyme defect. To fully understand the pathogenic mechanisms of hyperoxaluria, it would be important to know the relative

benefit in urinary oxalate excretion offered by dietary oxalate restriction and by increased calcium intake separately. A disproportionate rise in urinary oxalate excretion was observed when calcium supplements had to be reduced, while the patient was maintained a low-oxalate diet. This raises the possibility that hyperoxaluria may not be totally dependent of a high oxalate intake alone.

This patient needed a thiazide to control hypercalciuria and to prevent further worsening of the pre-existing osteoporosis. However, in this case, thiazide diuretics conferred several additional risks. In association with oral calcium supplements they induced hypercalcaemia and they aggravated hyperuricaemia. By inducing hypokalaemic intracellular acidosis, thiazide can aggravate the already existing hypocitraturia. Finally, as a consequence of the excess of acetyl-CoA, which is converted to cholesterol and fatty acids, severe hyperlipidaemia is a frequent manifestation of type 1-GSD [1]. Increases in total cholesterol, low-density lipoproteins, very low-density lipoproteins and total triglycerides were observed after short-term usage of thiazides [9]. Significant changes of HDL-cholesterol have not been reported. The exact mechanism for this lipid profile modification is not well understood, but an hypokalaemia-induced insulin resistance, with increased plasma levels of insulin, may contribute to an increase in triglyceride synthesis and increased production of free fatty acids [10]. Although some authors reported a normalization of the plasma lipid profile after long term use of thiazides [9], such a normalization was not confirmed by other authors. The use of thiazides on patients with type 1-GSD and underlying

severe hyperlipidaemia remains a matter of some concern.

Due to the various metabolic abnormalities involved, this case is a good example of the complexity of the treatment of renal stone disease associated with glycogen storage disease.

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