Hydrochlorothiazide reduces urinary calcium excretion in a child with Lowe syndrome

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Abstract

There is a growing recognition that children with Lowe syndrome are at risk of nephrocalcinosis and nephrolithiasis from hypercalciuria. Increased fluid intake and correction of metabolic acidosis have remained the focus for intervention but are not always successful. Thiazide diuretics, which reduce urinary calcium excretion, have not been used in these children, due to concerns that (i) they may not work as a result of the underlying tubular abnormalities and (ii) their risk may outweigh the potential benefits they have to offer. Herein we report a child with Lowe syndrome who was successfully treated with thiazides in managing his hypercalciuria.

Key words: nephrolithiasis, thiazides, tubulopathy, urinary calcium excretion

Background

The oculocerebrorenal syndrome of Lowe (Lowe syndrome) is a rare multisystem X-linked disorder resulting from mutations in the gene coding for an inositol 5-phosphatase, OCRL1 [1]. Clinical manifestations include ocular abnormalities (congenital cataracts, buphthalmos and nystagmus), neurologic symptoms (developmental delay, aggressive behavior, seizures and myopathy) and renal involvement. The renal involvement of Lowe syndrome is progressive and characterized by a proximal tubulopathy leading to Fanconi’s syndrome [2]. Treatment of this is supportive and involves correction of acidosis and supplementation of fluid and electrolytes such as potassium and phosphorous. Over time, in most patients glomerular filtration rate (GFR) declines in a slow and progressive manner, although some patients demonstrate a bi-phasic pattern of GFR decline; the mechanism of loss of renal function remains unclear [2]. Patients with Fanconi’s syndrome have generally been thought to be at a lower risk of stone formation and nephrocalcinosis in spite of having hypercalciuria (compared with those with distal renal tubular acidosis) due to their very dilute urine and elevated urinary citrate excretion [3]. However, there are some reports of children with Lowe syndrome developing nephrocalcinosis, in spite of correction of their acidosis [4, 5]. There are limited data on the use of thiazide diuretics in these children as a means to treating their hypercalciuria and preventing progression of nephrocalcinosis; moreover, concern has been raised regarding the safety and efficacy of using a medication that could further affect tubular function and lead to worsening electrolyte and fluid balance.

Herein we are reporting our experience in managing a child with Lowe syndrome who developed nephrolithiasis as a result of hypercalciuria and who was successfully managed with thiazides.

Case description

An 11-year-old boy with Lowe syndrome, followed in the pediatric nephrology practice since the age of 7.5 years, was brought in for the evaluation of a 1-week history of intermittent gross painless hematuria (bright red urine). He was otherwise asymptomatic; although his verbal communication skills were delayed, he did...
not appear in pain. His medications included 250 mg daily of phosphorous and 5 mEq/kg daily of oral potassium citrate; he had been on a stable dose of both medications for 18 months prior to his hematuria. He was polydipsic and polyuric, as expected, and had nocturnal enuresis, precluding precise quantitation of his urine output. His fluid intake was estimated by his mother to be around 3 liters a day. His electrolytes, when he presented with hematuria, were normal and notable for serum potassium of 3.6 mmol/L (3.6 mEq/L), bicarbonate of 26 mmol/L (mEq/L), total calcium of 2.5 mmol/L (9.9 mg/dL), phosphorus of 1.2 mmol/L (3.9 mg/dL) and uric acid of 181.4 µmol/L (3.3 mg/dL).

His estimated GFR (eGFR), based on the Schwartz calculation was 1.2 mmol/L (3.9 mg/dL) and uric acid of 181.4 µmol/L (3.3 mg/dL). During this time, timed urine collections were first detected. The first urine specimen, whether he experienced a change in his baseline urinary oxalate measurement, due to his inability to collect a timed urine specimen, was, at least in our patient, the gastrointestinal tract, as opposed to the tubule. The use of thiazide diuretics can be associated with hypokalemia and hyponatremia, to mention a few of their side effects, and therefore, they should be used with caution.

**Discussion**

Thiazide diuretics are a well-established treatment for hypercalciuria in calcium stone formers and have been shown, in long-term follow-up studied, to reduce the risk of recurrent stone formation [7]. The mechanism of action of thiazides has been extensively studied, both in animals and in humans. While much of the attention related to these agents has focused on their effects on distal tubular function, evidence from studies suggests a more complex mechanism of action. At a tubular level, it is hypothesized that by inducing mild volume depletion, thiazides increase proximal tubular resorption of water, sodium and calcium, thereby reducing urinary calcium excretion; this reduction in urinary calcium excretion has been demonstrated in an animal model [8]. In addition to reducing urinary calcium, thiazides have also been shown, by unclear mechanisms, to reduce gastrointestinal absorption of calcium and phosphorus; the net result of these is to promote a positive calcium balance in the body [8, 9]. Similar effects on phosphate retention were also noted in the same studies. Both of these effects lead to a reduction in the urinary supersaturation for calcium phosphate, as was seen in our patient. Inconsistent effects of thiazides on urinary oxalate excretion have been noted. In the genetic hypercalciuric stone-forming rat model, an increase in urinary oxalate excretion was seen and was presumed to be due to lower intestinal calcium bioavailability to bind to dietary oxalate and prevent it from being absorbed, since more of it would be bound to phosphorus present in the intestinal lumen [8]. Other studies, in humans treated with thiazides, have shown different results, with some showing a reduction in urinary oxalate excretion and others no change [10, 11]. Since our patient did not have a baseline urinary oxalate measurement, due to his inability to collect a timed urine specimen, whether he experienced a change in his urinary oxalate excretion over time could not be ascertained. However, it was reassuring that his urinary calcium oxalate supersaturation was normal on HCTZ. The mechanism of hypercalciuria in patients with Lowe syndrome is related to the proximal tubular dysfunction that is part of the underlying disease process, leading to urinary calcium wasting.

In summary, our report demonstrates the safety and efficacy of thiazide diuretics in reducing urinary calcium excretion and stabilizing the stone burden in children with Lowe syndrome. This occurred safely and in spite of an underlying tubulopathy, which may indicate that the major site of action of these agents was, at least in our patient, the gastrointestinal tract, as opposed to the tubule. The use of thiazide diuretics can be associated with hypokalemia and hyponatremia, to mention a few of their side effects, and therefore, they should be used with caution.
We feel that this case illustrates that thiazides, at least in low doses, can be safely used (or at least attempted) even in the presence of a tubulopathy such as Fanconi’s syndrome, to reduce urinary calcium excretion. Whether all children with Lowe syndrome (and others with Fanconi’s syndrome) who have hypercalciuria should receive a trial of thiazides to prevent stone formation or not remains to be determined.

Conflict of interest statement
None declared.

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