A novel mutation c.2010delG of CLCN5 gene associated with Dent disease-1 in an 11-year-old male with nephrolithiasis and nephrocalcinosis

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INTRODUCTION

Nephrocalcinosis is characterized by the deposition of calcium in the kidney parenchyma and tubules. It is associated with conditions that cause hypercalcemia, hyperphosphatemia, and the increased excretion of calcium, phosphate, and/or oxalate in the urine. According to the laboratory results, three groups can be formed in patients with nephrocalcinosis to make a differential diagnosis: hypercalcemia with hypercalciuria, hypercalcemia without hypercalciuria, and hyperphosphatemia with hyperphosphaturia [1].

Dent’s disease-1 is a rare case of hypercalciuria without hypercalciemia. It is characterized by low molecular-weight proteinuria, hypercalciuria, nephrocalcinosis or nephrolithiasis, proximal tubular dysfunction and renal failure in adulthood. Females are carriers and usually mildly affected. We present an 11-year-old child with nephrolithiasis and nephrocalcinosis with c.2010delG (or p.Asp671fs) mutation in CLCN5 gene which had not previously been reported in the Dent’s disease-1.

Keywords: child, tubulopathy, nephrolithiasis, nephrocalcinosis, Dent’s disease, CLCN5.


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CASE REPORT

An 11-year old boy was referred for nephrolithiasis and nephrocalcinosis. He denied any renal disease, trauma, diarrhea or constipation at past medical history. The grandmother had renal failure of unknown origin at medical family history. There was no pathological finding on the physical examination, including growth parameters and blood pressure according to age group. Laboratory findings were normal except hypercalciuria (9 mg/kg/d), 88% tubular phosphore reabsorption rate, low molecular weight proteinuria (B2 microglobulin 5080 mcg/L, n <250 mcg/L) in 24 hour urine, bilateral 4 mm non-obstructive nephrolithiasis and nephrocalcinosis at ultrasonography. Urinary oxalate, citrate, uric acid, serum bicarbonate, vitamin-D and parathormone values were also normal. Genetic analysis revealed the mutation c.2010delG (p.Asp671fs) in the CLCN5 gene that was detected in frame shift and identified as a stop codon (Figure). The patient was given potassium citrate and thiazide for persistent hypercalciuria.

DISCUSSION

The clinical diagnosis of Dent’s disease is based on the presence of LMW proteinuria, (elevation of B2-microglobulin, clara cell protein RBP – retinol-binding protein) and/or about five fold above the upper limit which is pathognomonic for Dent’s disease), hypercalciuria (>4 mg/kg per day characteristic for Dent’s disease) and diagnosis should include at least one of the presence: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia or chronic renal disease [6, 7]. Our patient fulfilled the criteria of the group of hypercalciuria without hypercalcemia rather than the groups of hypercalciuria with hypercalcaemia and hyperphosphaturia among the three groups of nephrocalcinosis. Distal renal tubular acidosis, medullar sponge kidney, neonatal nephrocalcinosis, loop diuretics, inherited tubulopathies, chronic hypokalemia and beta thalassemia are the underlying diseases in association with the group of hypercalciuria without hypercalcemia at nephrocalcinosis [1]. Normal blood pH, low molecular weight proteinuria, hypercalciuria and lower tubular phosphore reabsorption rate (TPR) without hypercalcemia pointed out inherited tubulopathy and Dent’s disease in our patient. Genetic analysis also confirmed the diagnosis with the mutation in CLCN5 gene.

The exact prevalence of Dent’s disease is undefined; to date, >250 families have been described [8]. Hypercalciuria and nephrocalcinosis are prevalent at a rate of 95% and 75% in affected males, respectively. Progression to end-stage renal failure are at the 3rd–5th decades of life in 30–80% of affected males [9]. In the absence of therapy targeting for the molecular defect, the current care of patients with Dent’s disease is supportive, focusing on the prevention of nephrolithiasis and nephrocalcinosis. Thiazide diuretics can be used to treat hypercalciuria [10, 11].

In summary, a new mutation c.2010delG (p.Asp671fs) in the CLCN5 gene that was first detected in frame shift and identified as a stop codon in our patient. Dent’s disease should be kept in mind in nephrocalcinosis with hypercalciuria, low molecular weight proteinuria and normal blood pH at male patients.

REFERENCES


Figure. The mutation c.2010delG (p.Asp671fs) in the CLCN5 gene


Поступила 27.12.17

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Received on 2017.12.27

Conflict of interest:
The authors of this article confirmed the absence conflict of interests, financial or any other support which should be reported.