Новая мутация c.2010delG гена CLCN5 при болезни Дента у 11-летнего мальчика, страдающего нефролитиазом и нефрокальцинозом

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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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Болезнь Дента-1 (ген CLCN5) наследуется редесивно, сцепленно с Х-хромосомой, и характеризуется протеинурией, гиперкальциурией, нефрокальцинозом, гиперфосфатемией и непараметрным сдвигом уровня калия. Женщины являются носителями и обычно страдают в большей степени. Мы исследовали наблюдение 11-летнего ребенка с нефролитиазом и нефрокальцинозом с мутацией c.2010delG (или p.Asp671fs) в гене CLCN5, которая ранее не была описана при болезни Дента-1.

У пациента проводилась диагностика постнатальной нефролитиаза в моче, мутация клеток, моче мочевина, бикарбонат мочи, витамины D и сульфатирия были в пределах нормы, но у пациента была высокая гиперкальциурия (уровень β-кроноблауна 5280 мкг/л, норма менее 250 мкг/л) в сутки, что свидетельствует о гиперкальциурии, которая является основным признаком нефролитиаза. Пациент был направлен к нефрологу с диагнозом нефролитиаз, нефрокальциноз.

Молекулярно-генетический анализ обнаружил мутацию гена CLCN5, c.2010delG (или p.Asp671fs) со сдвигом рамки, которая была идентифицирована как тонкая мутация (см. рисунок). Учитывая выраженную гиперкальциурию, пациент был направлен к нефрологу с диагнозом нефролитиаз, нефрокальциноз.

Почечный тубулярный акцедоз, дистальный тип, медуллярный и губчатая почка, нефрокальциноз, гиперкальциурия, гиперкальциурия, высокий уровень кальция в сутках, гиперкальциурия.

Новая мутация гена CLCN5 указывает на наследственную болезнь Клиническая картина пациента указывает на наследственную болезнь – болезнь Дента у нашего пациента. Генетический анализ также подтвердил диагноз – выявлена мутация гена CLCN5.

Ключевые слова: дети, нефролитиаз, протеинурия, нефрокальциноз, мутация Дента, CLCN5.

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Dent’s disease-1 (CLCN5) is a rare X-linked recessive tubulopathy characterized by low molecular weight proteinuria, hypercalcemia, nephrocalcinosis, nephrolithiasis, proximal tubular dysfunction and renal failure in adulthood. Females are carriers and usually mildly affected of Dent disease-1 mutation in CLCN5 gene which had not previously been reported in the Dent’s disease-1.

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

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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, hypercalciuria without hypercalcemia and hyperphosphaturia [1].

Dent’s disease-1 is a rare cause of hypercalciuria without hypercalcemia. It is characterized by low molecular-weight proteinuria, hypercalcemia, nephrocalcinosis, nephrolithiasis, and chronic renal failure. In about 60% of patients with X-linked nephrolithiasis, a mutation in the CLCN5 gene is detected (Dent disease type 1), whereas in 15%, the disease is due to a mutation in the OCRL gene (Dent disease type 2) [2–4]. Due to being X-linked, males are affected more severely, but females are carriers and usually only mildly affected in both forms of Dent’s disease [5].

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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 phosphate reabsorption rate, low molecular weight proteinuria (B2 microglobulin 5080 mcg/L), hyperkalemia and beta thalassemia are the underlying diseases in childhood nephrocalcinosis, loop diuretics, inherited tubulopathies, chronic acidosis, medullar sponge kidney, neonatal nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia and/or about five fold above the upper limit of the group 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, hyperkalemia, hypophosphatemia or chronic renal disease [6]. Our patient fulfilled the criteria of the group of nephrocalcinosis without hypercalciemia, rather than the group of hypercalciemia with hypercalcinemia and low phosphate among the three groups of nephrocalcinosis. Distal renal tubular acidosis, medullar sponge kidney, neonatal nephrocalcinosis, loop diuretics and inherited tubulopathies, chronic hypokalemia and beta thalassemia are the underlying diseases in association with the group of 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, hyperkalemia, hypophosphatemia or chronic renal disease [6]. Our patient fulfilled the criteria of the group of nephrocalcinosis without hypercalciemia rather than the group of hypercalciemia with hypercalcinemia and low phosphate among the three groups of nephrocalcinosis. Distal renal tubular acidosis, medullar sponge kidney, neonatal nephrocalcinosis, loop diuretics and inherited tubulopathies, chronic hypokalemia and beta thalassemia are the underlying diseases in association with the group of hypercalciuria.

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