Selective proximal renal tubular involvement and dyslipidemia in two cousins with oculocerebrorenal syndrome of Lowe

Rezan Topaloğlu[1], Michael Ludwig[2], Aslı Çelebi-Tayfur[1]

[1]Division of Pediatric Nephrology and Rheumatology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey, and [2]Department of Genomics, Institute for Clinical Chemistry and Pharmacology, Life and Brain Center, University of Bonn, Bonn, Germany. E-mail: rezantopaloglu@hacettepe.edu.tr

SUMMARY: Topaloğlu R, Ludwig M, Çelebi-Tayfur A. Selective proximal renal tubular involvement and dyslipidemia in two cousins with oculocerebrorenal syndrome of Lowe. Turk J Pediatr 2013; 55: 331-334.

Oculocerebrorenal syndrome of Lowe (OCRL) is a rare, X-linked disorder characterized by congenital cataracts, neonatal or infantile hypotonia, seizures, cognitive impairment, and renal tubular dysfunction. In this article, we report two maternal cousins with OCRL with a hemizygous p.Ala788Asp mutation in exon 22 of the *OCRL* gene. They presented with diverse features of selective proximal renal tubular defect and high serum levels of total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C).

Key words: cataract, dyslipidemia, novel mutation, selective proximal renal tubular defect, oculocerebrorenal syndrome of Lowe (OCRL).

Oculocerebrorenal syndrome of Lowe (OCRL) is a rare, X-linked disorder characterized by congenital cataracts, neonatal or infantile hypotonia, seizures, cognitive impairment, and renal tubular dysfunction[1,2]. The gene responsible for OCRL has been mapped to chromosome Xq26.1, and 23 exons and an alternatively spliced exon 18a encode a phosphatidylinositol 4,5-biphosphate 5-phosphatase (PtdIns[4,5]P2). The Ocrl protein is localized in the trans-Golgi apparatus, early endosomes and endocytic clathrin-coated pits, and regulates the pool of phosphatidylinositol 4,5-biphosphate, which plays an important role in cytoskeleton remodeling and cellular trafficking. Deficiency in this enzyme affects the intracellular protein sorting, especially within polarized cells like the renal epithelium and the lens[3,4]. Serum lipid profiles of patients with OCRL have been mentioned in isolated case reports[2,5]. Here, we report two maternal cousins with a novel hemizygous p.Ala788Asp mutation in exon 22 of the *OCRL* gene who showed different features of selective proximal renal tubular defect and high serum levels of total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C).

Case Report

Case 1

A newborn with low birth weight was referred to the Pediatric Nephrology Department of Hacettepe University for bilateral cataracts, nystagmus and proteinuria. He was born to nonconsanguineous parents. At presentation, his renal function tests, liver function tests, acid-base status, serum parathormone (PTH) levels, and renal ultrasound (USG) images were normal, and urine analysis revealed proteinuria [spot urine protein/urine creatinine (mg/mg): 2.5]. The ion exchange chromatography revealed aminoaciduria. He was operated for cataracts soon after admission. The weight and height of the patient remained below the 3rd percentile for age on the follow-up without obvious rickets. He also had moderate cognitive impairment. His renal functions gradually worsened and progressed to chronic renal failure at the age of 17 years. He showed no hypokalemia, hypophosphatemia or overt acidosis up to developing renal failure. The formal urine glucose determinations were always below the threshold. He maintained normal serum phosphate levels despite his abnormally low maximum tubular reabsorption of phosphate per unit volume of glomerular

filtration rate (TmP/GFR=3.1 mg/dl). The recent laboratory investigations demonstrated impaired renal function (blood urea nitrogen [BUN]: 30.6 mg/dl, serum creatinine: 1.58 mg/dl, estimated GFR (eGFR): 29 ml/min/1.73 m2) (eGFR was calculated by Schwartz-Haycock formula; k value was accepted as 0.28 as determined in a study evaluating the renal phenotype in patients with *OCRL*[6]). He had normal serum electrolyte, magnesium and PTH levels, high serum levels of total cholesterol (281 mg/dl, normal: 200 mg/dl), LDL-C (187 mg/dl, normal: 130 mg/dl), and HDL-C (77 mg/dl, range: 40-60 mg/dl), and increased levels of urine protein (1272 mg/l/day) and urine β2 microglobulin (20.000 ng/ml). The genetic mutation analysis revealed a hemizygous p.Ala788Asp (numbering according to ENSEMBL transcript ID ENST00000371113) mutation in exon 22 of the *OCRL* gene (Fig. 1). Angiotensin converting enzyme inhibitor (ACE-I) was initiated for proteinuria, but the patient was noncompliant to receive the medication regularly. Recently, he had been using only rosuvastatin calcium (5 mg/day) for hypercholesterolemia.

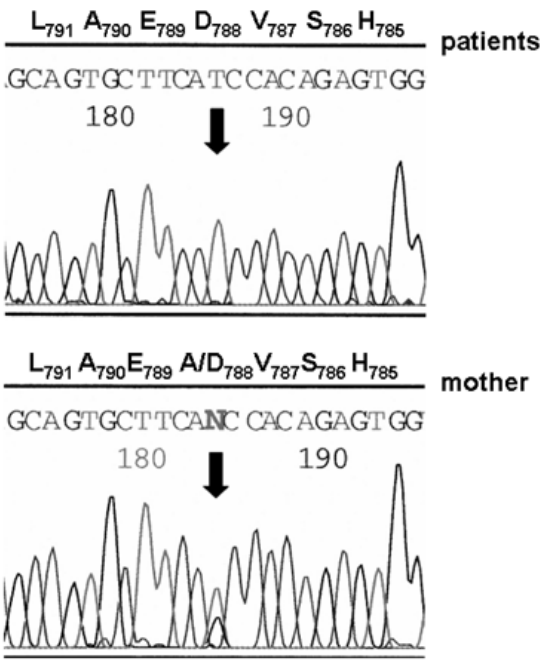

Fig. 1. Sequence analysis (reverse sequencing reaction is shown) of the *OCRL* gene in both patients and the mother of Case 2. The mutation detected is indicated by an arrow with the amino acids encoded given above.

Case 2

The patient, aged 2 months, was referred to the Pediatric Nephrology Department of Hacettepe University for bilateral cataracts, nystagmus and proteinuria [spot urine protein/urine creatinine (mg/mg): 2.6]. He was born to nonconsanguineous parents. In his family history, his maternal cousin (Case 1) was diagnosed as OCRL. Birth length and weight were within normal range, but short stature became evident at 2 years of age. At presentation, his renal function tests, liver function tests, acid-base status, serum PTH levels, and renal USG images were normal. The ion exchange chromatography revealed no aminoaciduria. Growth parameters were below the 3rd percentile after 1 year of age without obvious rickets. He also had moderate cognitive impairment. He underwent surgeries for bilateral cataracts and bilateral glaucoma at 2 months of age and 5 years of age, respectively. The patient had no hypokalemia, hypophosphatemia or acidosis at the presentation or during the follow-up. At 5 years of age, hypercalciuria (4.6 mg/kg/day) and proteinuria (776 mg/day) were remarkable. The formal urine glucose determinations were always below the detection threshold. Despite elevated urinary phosphate excretion (TmP/GFR: 2.87 mg/dl), he maintained normal serum phosphate levels. The recent laboratory investigations demonstrated a decrease in renal function (BUN: 17.7 mg/dl, serum creatinine: 0.95 mg/dl, eGFR: 45.9 ml/min/1.73 m^2), normal serum electrolyte, magnesium, PTH, and bicarbonate levels, high serum levels of cholesterol (212 mg/dl) and HDL (75 mg/dl), and increased urinary excretion of calcium (7.8 mg/kg/day), protein (1056.72 mg/day) and β2 microglobulin (50.000 ng/ml). Despite the hypercalciuria, the recent abdominal USG image was normal. The genetic mutation analysis of Case 2 revealed a hemizygous p.Ala788Asp mutation in exon 22 of the *OCRL* gene as well and showed the mother to be a carrier of the c.C2363A nucleotide transversion (Fig. 1). Pravastatin sodium (10 mg/day) for hypercholesterolemia, enalapril (5 mg/day) for proteinuria and hydrochlorothiazide for hypercalciuria were initiated.

Discussion

Clinical features of *OCRL* include hypotonia with absent deep tendon reflexes and cataracts present at birth, short stature and failure to thrive evident by age 1 to 3 years, glaucoma and corneal keloids, developmental delay, and abnormal behavior[1,2]. Laboratory studies show renal tubular dysfunction. Aminoaciduria, phosphaturia and proteinuria are typically observed. Glucose is absent or occasionally detected in the urine. Hyperphosphaturia, hypercalcuria and metabolic acidosis may lead to osteomalacia and rickets. Nephrocalcinosis, nephrolithiasis or urolithiasis may develop. The acidemia and hypokalemia are caused due to the loss of bicarbonate, phosphate and sodium[6,7]. The measurement of enzyme activity in cultured fibroblasts and the mutational analysis confirm the diagnosis[1,3].

There is a wide clinical variability among patients. However, only a few reports in the literature are focused on serum lipid profiles of these patients. Since the patients with OCRL have increasingly prolonged survival, dyslipidemia is an important risk factor for long-term complications.

Both of our patients presented with selective tubulopathy. While they both had high levels of urinary β2 microglobulin, they showed no hypokalemia, hypophosphatemia, overt acidosis, or glucosuria on presentation or during the follow-up. Thus, the urinary excretion of calcium was within normal range in Case 1. The urinary excretion of calcium was evident in Case 2, but renal USG imaging did not reveal nephrocalcinosis. Bockenhauer et al.[6] suggested calcium reabsorption in OCRL might be secondary to abnormal intracellular trafficking in the proximal segment, and the finding of nephrocalcinosis in renal USG imaging did not correlate directly with the degree of hypercalcuria. The results of urinary glucose determinations of both patients were negative, repeatedly. Absence of glucosuria in patients with OCRL had been reported in other studies[6,7]. None of the patients in the study of Bockenhauer et al.[6] had glycosuria, even when study conditions were modified to account for polyuria. Furthermore, the authors suggested a selective proximal tubulopathy for OCRL in the presence of hypercalcuria and in the absence of glucosuria.

The *OCRL* mutations causing OCRL occur primarily in exons 8-23[8]. The two patients reported here showed a novel p.Ala788Asp mutation in the RhoGAP-like domain of the OCRL protein. Several other missense mutations affecting this motif have been observed9; however, dyslipidemia was not reported in any of those patients. To date, serum lipid profiles of patients with OCRL have been mentioned only in a single case report and in a series of patients[2,5]. Charnas et al.[2] reported high total cholesterol levels mainly due to elevated HDL-C levels in 15 of 23 patients with OCRL (62.5%); the mean serum triglyceride concentration of the patients with OCRL was normal. The plasma cholesteryl ester transfer protein (Cept) is an important protein in HDL-C metabolism as it promotes the transfer of cholesteryl esters for triglycerides from HDL-C to ApoB-containing lipoproteins[9]. Thus, Asami et al.[5] claimed the association of a heterozygous *CEPT* mutation (p.Asp442Gly mutation in exon 15 of the *CEPT* gene) in one of three OCRL patients who had increased serum HDL and apo-A1 levels; however, this observation was not further confirmed. Moreover, since this mutation is found to be present in 7% of a random sample of Japanese men, it may resemble a benign single nucleotide polymorphism (SNP).

The prevalence of hyperlipidemia or dyslipidemia in patients with chronic renal disease (CRD) is higher than in the general population. The severity of dyslipidemia correlates directly with the degree of proteinuria and inversely with the serum albumin. Reduced GFR is also associated with hyperlipidemia. The patients with predialysis CRD usually have increased levels of triglycerides and VLDL-C, decreased levels of HDL-C, and no consistent change in the level of LDL-C[10]. The serum lipid profile of Case 1 was different from those seen in patients with CRD. Both of our patients had high levels of total cholesterol, LDL-C and HDL-C. The serum lipid electrophoresis of Case 1 and Case 2 showed an elevation in β lipoprotein fraction (comprised by transferrin) and in α lipoprotein fraction (comprised by HDL-C), respectively. The dyslipidemia in the two patients might have been due to either the metabolic effects of OCRL, familial genetic factors, or different combinations of these factors.

REFERENCES

1. Loi M. Lowe syndrome. Orphanet J Rare Dis 2006; 1: 16.
2. Charnas LR, Bernardini I, Rader D, Hoeg JM, Gahl WA. Clinical and laboratory findings in the oculocerebrorenal syndrome of Lowe, with special reference to growth and renal function. N Engl J Med 1991; 324: 1318-1325.
3. Attree O, Olivos IM, Okabe I, et al. The Lowe's oculocerebrorenal syndrome encodes a protein highly homologous to inositol polyphasphate-5-phosphatase. Nature 1992; 358: 239-242.
4. Oooms LM, Horan KA, Rahman P, et al. The role of the inositol polyphosphate 5-phosphatases in cellular function and human disease. Biochem J 2009; 419: 29-49.
5. Asami T, Inano K, Miida T, Kikuchi T, Uchiyama M. Two families of Lowe oculocerebrorenal syndrome with elevated serum HDL cholesterol levels and CEPT gene mutation. Acta Paediatr 1997; 86: 41-45.
6. Bockenhauer D, Bokenkamp A, Van't Hoff W, et al. Renal phenotype in Lowe syndrome: a selective proximal tubular dysfunction. Clin J Am Soc Nephrol 2008; 3: 1430-1436.
7. Cho HY, Lee BH, Choi HJ, Ha IS, Choi Y, Cheong HI. Renal manifestation of Dent disease and Lowe syndrome. Pediatr Nephrol 2008; 23: 243-249.
8. Hichri H, Rendu J, Monnier N, et al. From Lowe syndrome to Dent disease: correlations between mutations of the OCRL1 gene and clinical and biochemical phenotypes. Hum Mutat 2011; 32: 379-388.
9. McCaskie PA, Beilby JP, Chapman CML, et al. Cholesteryl ester transfer protein gene haplotypes, plasma high-density lipoprotein levels and the risk of coronary heart disease. Human Genet 2007; 121: 401-411.
10. Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms and potential consequences. Am J Physiol Renal Physiol 2006; 290: F262-F272.