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Case report

A Boy with Dent-2 Disease

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A B S T R A C T

Dent-2 disease is an X-linked renal tubulopathy associated with mutations in OCRL gene. It is characterized by low-molecular weight proteinuria, hypercalciuria, nephrolithiasis/nephrocalcinosis and progressive renal failure. Patients may have some extra-renal symptoms of Lowe syndrome, such as peripheral cataracts, mental impairment, stunted growth or elevation of creatine kinase/lactate dehydrogenase. Our patient was suspected to suffer from Dent disease at 8 months of age because of proteinuria and hypercalciuria. He had no prominent extra-renal symptoms. OCRL mutation in exon 1 (c.217_218 del TT p.L73F, fs X1) was found. He was treated with amiloride+hydroclorthiazide and citrate with good results in reducing calciuria. His renal ultrasound, ophthalmologic and cardiologic examinations, mental development and other laboratory findings are normal till date.

Key words: *Dent-2 disease, OCRL mutation, hypercalciuria, proteinuria*

Introduction

Dent disease[1] is an X-linked tubulopathy characterized by low-molecular weight (LMW) proteinuria (in 100%), hypercalciuria (in 90%), nephrolithiasis/nephrocalcinosis (in 75% of the patients) and progressive renal failure. The disorder has been reported in around 250 families, however, its prevalence is still unknown[2]. Around 60% of the patients have mutations in the *CLCN5* gene. They have Dent-1 disease caused by mutations affecting the voltage-gated chloride channel and chloride/proton antiporter (CIC-5), predominantly expressed in the proximal tubule and α-intercalated cells of the collecting duct[3]. About 15% of patients have mutations in the OCRL gene located on chromosome Xq25, which also causes Lowe oculocerebrorenal syndrome[4]. There is a phenotypic continuum within patients with Dent-2 disease and Lowe syndrome. Affected children may have some of the extra-renal symptoms of Lowe syndrome, such as peripheral cataracts, mental impairment, stunted growth or elevation of creatine kinase/lactate dehydrogenase[3,4]. The OCRL protein localizes to lysosomes and the trans-Golgi network[5], early endosomes, plasma membrane ruffles and clathrin-coated trafficking intermediates. It works as a phosphoinositol 5-phosphatase that helps regulate the pools of phosphatidyl-inositol 4,5-bisphosphate in the cell[6]. The OCRL protein is expressed in several tissues, including the kidney, eye and brain that are clinically affected in Lowe syndrome[5]. Shrimpton et al.[7] proposed a model in which the different mutation spectra for Dent-2 disease *versus* Lowe syndrome reflects an underlying mechanism that explains the phenotypic differences between the two diseases. Almost all Dent-2 mutations fall into two classes: either mild, with OCRL expressed but functioning at a reduced level (missense mutations in the phosphatase domain) or truncating mutations, with little or no expression or function when studied in skin fibroblasts (frameshift and stop mutations in exons 1–7)[8]. Two mutations initially reported as causing Dent-2 disease were identified in patients with Lowe syndrome thus extending the clinical variability of OCRL mutations[3]. All possible phenotypic variabilities, treatment options and prognosis of patients with Dent-2 disease are still not fully understood.

Case Report

Our patient is a boy born in March 2007. His family history is negative for kidney diseases. His birth weight

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was 3250 g and length 49 cm. He was treated for bacteriuria (E. coli) in the maternity ward. At the age of 1.5 month he was admitted to hospital because of urinary tract infection. After that he had persistent proteinuria and hematuria so he was sent to our Department of Nephrology. At the admission he was in the eighth month of life. His body mass was 7100 g and length 68 cm. He had a mild shoulder girdle muscle hypotonia, large and protruding ears, epicanthus and telecanthus, smaller mandible and longer filtrum. Besides that, he looked healthy. From the laboratory tests performed, we highlighted hypercalciuria (up to 8.29 mg/kg/24 hours or calcium/creatinine ratio up to 2.1), proteinuria from 0.59 g up to 2.46 g in 24 hours, urinary albumin 314.9 mg/l, urinary β2 microglobuline 3.84 mg/l and serum PTH<0.2 pmol/l. Renal ultrasound and voiding cystourethrography, performed because of recurrent urinary tract infections, showed normal findings as well as cardiologic and ophthalmologic examination. At that time, we suspected that the boy was suffering from Dent disease. At the age of 17 months, he was admitted to our Department for the second time. He had persistent hypercalciuria and tubular proteinuria. Renal scintigraphy showed a symmetrical tubular damage. We performed renal biopsy and found histologically normal glomeruli and densely packed tubules. Interstitium was only at two places permeated by abundant connective tissue. Patient's mother and his 3.5 years old brother had normal global renal function and renal ultrasound finding. They had no hypercalciuria or proteinuria. At the age of 17 months, we started to treat our patient with combination of amiloride and hydrochlorthiazide and citrate. When his was 2.5 years old, genetic analysis was completed and OCRL mutation in exon 1 (c.217_218 del TT p.L73F, fs X1) was found, thereby providing evidence that he is affected with Dent-2 disease. This variant was formerly reported as c.166_167 del TT p.L56D, fs X57. We also confirmed that the patient's mother is a carrier and that his brother and grandmother do not have this mutation. When our patient was 3 years old he underwent brain magnetic resonance imaging which showed normal finding. We continued therapy with diuretics and citrate but we stopped giving him vitamin D. During year 2010 calcium/creatinine in his spot urine was 0.61, 0.95, 0.93 and 0.83. At his last control (age 3 years and 10 months) he had normal global renal function and renal ultrasound. Proteins were 0.83 g in a 24-hours urine sample, α1 microglobuline 185 mg/l and urine calcium/creatinine ratio between 0.36 and 0.65 (in mmols), calcium pro kilos in 24-hours urine was 1.89 mg (Table 1).

Discussion

Although, since 1964, when Dent and Friedman[1] reported 2 boys with rickets associated with renal tubular damage characterized by hypercalciuria, proteinuria, hyperphosphaturia and aminoaciduria, many authors have written about the phenotypic variability and new gene mutations[2–4,7,9,10], treatment options[9,11,12] and prognosis of patients with Dent disease, it is still a challenge. There is a wide overlap of renal symptoms between Dent-1 and Dent-2 disease and Lowe syndrome[3]. Analysis of OCRL mutations show that most Dent 2 mutations fall into two classes that do not overlap with Lowe mutations[7]. On the other hand, it must be kept in mind that mild and severe presentations of Lowe syndrome together with pure renal forms of Dent disease were associated with a complete loss of the OCRL enzymatic activity. A possible explanation of this clinical variability might be the presence of modifying factors (compensatory phosphatases, interacting proteins etc) whose expression will depend on the genetic background of the different patients[13]. Nephrocalcinosis seems to be more prevalent in Dent-1 disease and renal tubular acidosis, aminoaciduria and renal failure in Lowe syndrome. Patients with Dent-2 disease show an intermediate phenotype. Nephrolithiasis usually takes the form of nephrocalcinosis[3]. It is thought that the decline in renal function may be partially due to the infection and obstruction. Authors reported connection between hypercalciuria and reccurent urinary tract infections (Biyikli et al.) and some noticed that reduction in urinary calcium excretion resulted in no futher infections (Vachvanichsanong et al.)[14]. This however, cannot be the sole reason. Some authors reported interstitial fibrosis, glomerular hyalinosis, tubular cell changes and focal glomerulosclerosis found at renal biopsy[15,16]. Given this, efforts have been made in defining the best treatment that would suppress hypercalciuria and the formation of stones, but also have protective action in terms of delaying interstitial fibrosis and renal failure[2,9,11,12]. Treatment with thiazide diuretics in combination with amiloride, citrate and angiotensin-converting enzyme inhibitor might be useful[9].

Our patient was suspected to suffer from Dent disease at 8 months of age because of LMW proteinuria and hypercalciuria. He did not have any prominent extra-renal manifestations except mild hypotonia. OCRL mutation in exon 1 (c.217_218 del TT p.L73F, fs X1) was found. This mutation was previously discovered in one patient by A. E. Shrimpton and colleagues in 2009[7]. Their patient was 2.5 years old at the time of diagnosis, he had LMW proteinuria, hypercalciuria and hematuria. His renal function was normal, he had no renal stones, no cataracts, no mental impairment or hypotonia. He did not have aminoaciduria, glycosuria, rickets, hypokalemia and hypomagnesemia at the age of diagnosis, the same as our patient. Although there is currently no therapeutic modality which was shown to slow the progression of renal disease in patients with Dent-2 disease, we started treatment with amiloride+hydroclorthiazide and K-Na citrate and got a good response in reducing calciuria. Therapy was discontinued from October 2009 by January 2010 so calciuria increased to over 5 mg/kg/day. After the reintroduction of drugs calciuria is now again within acceptable limits for age[17,18] and circumstances. His creatinine, plasma bicarbonate and serum electrolyte levels are within normal values. We observed that the value of copper in serum was several times on the top or slightly

TABLE 1
MAJOR FINDINGS AND TESTS DURING THE FOLLOW-UP OF PATIENT

	8 months	17 months	22 months	2 years 7 months	3 years	3 years 10 months
Creatinine (μmol/l)	41	37	37	50	51	53
(ref. val.)	35–62	35–62	35–62	35–62	35–62	44–71
Plasma bicarbonates (mmol/l)	22	23.1	25.4	20.7	25.1	22.7
(ref. val.)	21–27	21–27	21–27	21–27	21–27	21–27
LDH (U/l)	304	–	334	293	355	315
(ref. val.)	150–360	150–360	150–360	150–360	150–360	150–360
CK (U/l)	57	–	255	101	212	161
(ref. val.)	60–305	60–305	60–305	60–305	60–305	75–230
Serum electrolytes	normal	normal	normal	normal	normal	normal
Copper (μmol/l)	17.4	28.9–30.8	25.2	25.7	23.0	25.5
Calciuria (mg/kg/day)	8.29	5.17	5.01	2.47	5.03	1.89
(ref. val.)	5		4	4	4	<4
Ca/cr (mmol)	2.10	1.20–4.94	2.14	0.48	0.71–2.01	0.36–0.65
(upper limit)	1.69	1.69	1.18	1.18	1.18	1.18
Proteinuria (g/dU)	2.46	0.83	0.80	0.17	0.92	0.83
(ref. val.)	0.15	0.15	0.15	0.15	0.15	<0.15
β2 microglob. (mg/l)	3.84	3.12	–	2.17	–	α1=185
(ref.val.)	0.8–2.2	0.8–2.2	0.8–2.2	0.8–2.2	0.8–2.2	α1 15
Glycosuria	no	no	no	no	no	no
Aminoaciduria	no	no	–	no	–	–
PTH (pmol/l)	<0.2	1.7	<0.2	<0.2	–	1.3
(ref.val.)	1–6	1–6	1–6	1–6	1–6	1–6
25-OH vit. D (nmol/l)		–	–	80.67	69.79	30.71
(ref. val.)	≥75	≥75	≥75	≥75	≥75	≥75
Renal ultrasound	normal	normal	normal	normal	–	normal
Ophtalmologic examination	normal	normal	–	normal	–	–
Cardiologic examination	normal	ECG Normal	–	normal	–	–
Weight (kg)	7.1	10	10.5	11.7	13.3	14
(percentile)	<5	5–10	5–10	5–10	10–25	10–25
Height (cm)	68	74	79	90	94	95
(percentile)	10–25	<5	<5	10–25	10–25	5–10
Treatment ailoride-hydrochlorthiazide and K-Na citrate	no	started 16. 10. 2008.	yes+D vit.	yes+D vit.	no therapy was discontinued during 3 months before this control	yes
Other examinations		renal scintigraphy (DMSA) + renal biopsy		renal scintigraphy (DTPA) GFR=84 ml/min/m^2	brain MRI	

(ref.val.) = referent values for age

above the upper limit of normal ranges, for which we have no explanation. We noticed that the boy is somewhat less advanced in body weight and height (5th–10th centile for age). According to the article of Bökenkamp and colleagues, patients with Dent-2 disease and Lowe syndrome were shorter than those with Dent-1 disease[3].

Psychological testing at age 15 months and 3 years recorded appropriate mental development for age. His renal ultrasound, ophthalmologic and cardiologic examination remained normal. In a previous study, patients having Dent-2 disease with eye involvement were aged 13 and 6 years in the time of diagnosis[3] and were older than

our patient. Also, renal biopsy in our patient did not reveal the changes that have been described by other authors[15,16]. The diagnosis was established in a very young patient so it is possible that other phenotypic features may manifest later in life. Or he would not have developed them anyway? Can we slow the progression of the disease? We will continue treatment with diuretics and citrate and naturally, regular controlling of our patient. In the future we will consider the introduction of ACE inhibitors.

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DJEČAK SA DENT-2 BOLEŠĆU

SAŽETAK

Dentova bolest tip 2 je X-vezana tubulopatija udružena s mutacijama u *OCRL* genu. Karakterizirana je niskomolekularnom proteinurijom, hiperkalciurijom, nefrolitijazom/nefrokalcinozom i progresivnim bubrežnim zatajenjem. Bolesnici mogu imati i neke ekstrarenalne simptome vezane uz sindrom Lowe, kao što su periferna mrena, mentalno oštećenje, slabiji rast i povišenje vrijednosti enzima kreatin kinaze/laktat dehidrogenaze. U našeg bolesnika se posumnjalo da boluje od Dentove bolesti u dobi od 8 mjeseci zbog proteinurije i hiperkalciurije. Nije imao značajnijih ekstrarenalnih simptoma. Nađena je OCRL mutacija u eksonu 1 (c.217_218 del TT p.L73F, fs X1). Liječen je kombinacijom amilorida i hidroklortiazida te citratima s dobrim rezultatima u smanjivanju kalciurije. Ultrazvuk bubrega, okulistički i kardiološki pregledi, mentalni razvoj kao i drugi laboratorijski nalazi su mu do sada uredni.