Dent disease

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Abstract

Dent disease is an x-linked disorder of proximal renal tubules that occurs almost exclusively in males. It is clinically characterized by significant, mostly low-molecular weight proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and chronic renal disease. The signs and symptoms of this condition appear in early childhood and worsen over time. There are two forms of Dent disease, which are distinguished by their genetic cause and pattern of signs and symptoms (type 1 and type 2). Dent disease type 2 is characterized by clinical features described above and is also associated with extrarenal manifestations, such as mild intellectual disability, hypotonia and cataract. Some researchers consider Dent disease type 2 to be a mild variant of Lowe syndrome.

In this article, a clinical case of a boy with significant proteinuria in the nephrotic range and hypercalciuria is presented. Genetic analysis confirmed Dent disease type 1.

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Introduction

Dent disease is an inherited, X-linked condition that affects the proximal tubules of the kidney. Clinically it is characterized by significant proteinuria, with mostly low-molecular weight proteins excreted in urine. The excretion of albumins is increased in glomerular disorder, whereas in tubular disorder the excretion of alpha-1-microglobulin, beta-2-microglobulin, retinol-binding protein and N-acetyl glucosaminidase is increased. Dent disease is also characterized by hypercalciuria, nephrocalcinosis and nephrolithiasis. It is a chronic disease that can progress to end stage renal disease (1-3). It is a very rare inherited disease. In literature, the frequency of the disease has not been exactly determined: 250 families with Dent disease type 1 and 25 individuals with Dent disease type 2 have been diagnosed worldwide. The disease can be fully expressed only in males since the inheritance is X-linked recessive. In females the disease is clinically expressed in a mild form. Females are carriers of the disease, in 50 % they pass it to sons and in 50 % to daughters. In 10 % the disease is caused by a new mutation. Also in these cases, the inheritance of the disease to successive generations is X-linked recessive (2) and is usually manifested as asymptomatic significant tubular proteinuria and/or hypercalciuria in boys older than 10 years of age. From 30 % to 80 % of affected males develop end stage renal disease aged 30 to 50 years. In some of them it is developed in late adulthood around the age of 60 years (1). It is often accompanied with rachitis, osteomalacia, and

poor growth. It can be inherited in two ways. The first and more common one is Dent disease 1 with mutations in the *CLCN5* gene, the second one is Dent disease 2 with mutations in the *OCRL* gene, which is additionally associated with extrarenal abnormalities (mild intellectual disability, cataract and hypotonia) (1-5).

We present a case of a boy with significant proteinuria in the nephrotic range who started being treated at the age of three years. The determination of the type of proteinuria revealed a mixed, glomerular proteinuria in combination with abundant tubular proteinuria. Proteinuria in the nephrotic range was caused mainly by albuminuria, as tubular proteinuria usually does not exceed the nephrotic threshold. The boy also had a pronounced normocalcemic hypercalciuria. Genetic analyses confirmed Dent disease type 1.

Case presentation

A 3-year-old boy was referred to the Department of Nephrology at the University Children's Hospital from a regional hospital due to proteinuria in the nephrotic range in 2008.

The family history revealed that the grandfather had chronic chronic kidney disease. Due to severe significant proteinuria at the age of 18, he underwent renal biopsy that showed a segmental sclerosing glomerulopathy. At the age of 44, the grandfather had end stage renal disease; currently he has a transplanted kidney. The grandfather's mother had renal disease as well. The boy was born as the second child after his mother's second, normally progressing pregnancy, with normal measurements at birth. The period after birth was uneventful. For frequent respiratory infections he received beta-lactam antibiotics many times. Until hospitalization at the Department of Nephrology he recovered from infectious mononucleosis and had surgery due to phimosis and testicular retention. He recovered from streptococcal tonsillitis, two middle ear inflammations, gastroenteritis with paralytic ileus and atypical pneumonia. He had no allergies, was vaccinated according to the vaccination schedule, and had chicken pox.

At his health check when he was 3 years old, he was diagnosed with proteinuria. His parents had been noticing for some time that his morning urine was cloudy without macrohaematuria. The boy looked healthy and had no swellings. In a regional hospital the proteins in the 24-hour urine were in the nephrotic range (0.64 g/day = 40 mg/m^2/h). Urine sediment and creatinine (44 µmol/L) were within the normal range.

At the first check-up at our clinic, quiet systolic murmur 2/6 was heard but otherwise the clinical examination was uneventful. The growth was appropriate for the age. His blood pressure was normal. Laboratory examinations showed slightly elevated sedimentation values (30 mm/h) and mild thrombocytosis (thrombocytes 425). Acid-base status showed mild compensated metabolic acidosis. Serum creatinine (47 µmol/L) and urea (3.5 mmol/L) values were normal, including creatinine clearance (116.8 ml/min/1.73 m^2) and serum electrolytes. Native urine results showed proteinuria (2+) and microscopic haematuria (32 erythrocytes), urine pH was 7. The 24-hour urine collection showed proteinuria in the nephrotic range (1.7 g = 107 mg/m^2/h). The determination of the type of proteinuria in urine revealed a mixed, selective glomerular proteinuria with an elevated albumin excretion (albumin/creatinine 104.38; normal up to 2.26 g/mol) and IgG (IgG/creatinine 20.0; normal up to 1.13 g/mol) accompa-

nied with abundant tubular proteinuria with a higher excretion of alpha-1-microglobulin (alpha-1-microglobulin/creatinine 72.19; normal up to 1.58 g/mol). The ratio of IgG to albumins (IgG/alb) was 0.19. Beta-2-microglobulin value in serum was normal, however it was significantly elevated in urine (94.6; normal up to 0.3 mg/l). CRP, haemogram, hepatogram, serum protein electrophoresis and lipidogram were normal as well.

The fractional excretion of electrolytes in urine was determined, and elevated potassium excretion and hypercalciuria were established (11 mg/kg/day; upper level 4 mg/kg/day). Fractional excretions of other electrolytes were normal.

The values of complement, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies and cytoplasmic antigens, anti-DNA and anti-cardiolipin antibodies were negative.

Abdomen and urinary tract ultrasound scans were normal, without signs of nephrocalcinosis or kidney stones (Figure 1; A).

Renal biopsy which was performed at the beginning of 2009 showed that the boy had inherited nephropathy with prevalent chronic striped tubulointerstitial histopathological changes and with nonspecific chronic poorly active fibrosing (50–60%) tubulointerstitial nephritis in striped pattern with extensive secondary changes in Malpighian bodies with pericapsular fibrosis at interstitial events. Glomerular changes were mild, collapsing with accompanying hypertrophic podocytes; they resembled a collapsing type of focal segmental glomerulosclerosis (FSGS). The aforementioned changes were most possibly the secondary, and tubulointerstitial events the primary cause of their occurrence. Renal biopsy in 2009 showed no signs of microscopic nephrocalcinosis. A je to ista biopsija kot na začetku odstavka, ali je bila narejena še ena v istem letu?

Considering the clinical features and the laboratory results, Dent disease was suspected; however the only way to prove it was genetic-molecular diagnostic testing, which was performed revealing a mutation of the *CLCN5* gene; the boy had it in hemizygous form as the disease is inherited recessively and is X-linked.

Due to pronounced hypercalciuria, the boy underwent bone density measurements, which confirmed osteopoenia; upon endocrinologist's advice, D3 vitamin and calcium citrate were introduced. Increased fluid intake (over two litres of liquid a day) and restricted salt intake were recommended; additionally, the treatment with a combination of thiazide and amiloride as well as potassium citrate was introduced to decrease calcium excretion with urine and equally to prevent possible hypokalaemia. As proteinuria was mixed, angiotensin-converting-enzyme inhibitor (ACE inhibitor) was introduced to decrease glomerular proteinuria.

The boy is being regularly monitored at the Department of Nephrology. He has densitometry once a year, his growth dynamics is being monitored by endocrinologist. Bone density has normalized with adequate therapy. Acid-base status has been normal. Renal function has been normal, with creatinine increase at the end of 2016, yet still within the normal range. Significant proteinuria persists; it has progressed to non-selective glomerular proteinuria with abundant tubular proteinuria (IgG/albumin ratio over 0.2). Calciuria decreased gradually, only in the last few months it has slightly increased, which can be attributed to transitional discontinuance of thiazide and amiloride. Over the last few years, mild microscopic haematuria has been

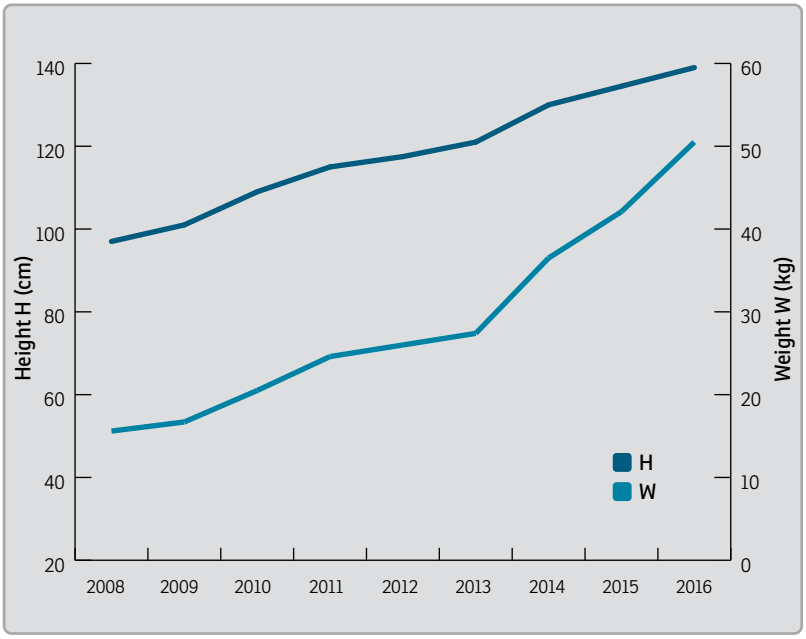

Figure 1: Body growth and weight in years 2008–2016

present in urine. Figures 1 and 2 show body growth, renal function, proteinuria and calciuria in the boy from 2008 when the treatment began until 2016.

Ultrasound scan in 2016 showed initial signs of nephrocalcinosis (Figure 3; B).

Discussion

Dent disease is an inherited, X-linked recessive renal tubular disease, also called X-linked recessive hypercalciuric hypophosphatemic rachitis characterized by significant proteinuria (increased low-molecular weight proteins in urine), hypercalciuria and nephrocalcinosis (1-3). The disease is almost exclusively found in males. A pathological variant in the *CLCN5* gene accounts for 60 % of people suffering from the disease (Dent disease 1); the other pathological variant is in the *OCRL* gene, and it accounts for 15 % of people suffering from the disease (Dent disease 2) (1-5). Due to X-chromosome inactivation, chronic renal disease rarely affects women who are carriers of this disease, and in most cases the disease is manifested only as hypercalciuria (1,2).

The disease is suspected when the following three criteria are present (1-3,6):

1. Significant tubular low-molecular weight proteinuria: characterized by 5 to 10 times higher values than normal; measurements of proteins alpha-1-microglobulin, beta-2-microglobulin, retinol-binding protein and N-acetylglucosaminidase.
2. Hypercalciuria: > 4 mg/kg calcium in 24 hours (children > 2 years and adults) or 0,25 calcium/creatinine mg/mg (= 0,57 mmol/mmol) in single urine collection (patients over 18 yars; for children there are different reference tables which are age dependent).
3. At least one of the following criteria is fulfilled: hypophosphatemia, chronic renal disease, family history of X-linked inherited disease, nephrolithiasis (kidney stones: Ca oxalate and/or Ca phosphate), haematuria (microscopic or macroscopic) and nephrocalcinosis (deposition of calcium salts in the medulla of the kidney or rarely in the renal cortex) (6). When ultrasound shows nephrocalcinosis, further investigations to determine the cause of the disease are needed. Electrolytes, including calcium and phosphate, urine acidity as well as urea and creatinine values in serum need to be determined. If the aforementioned investigations are normal and there are no signs of hypercalcemia (exclusion of primary hyperparathyroidism, sarcoidosis, vitamin D3 treatment,...) and distal tubular acidosis, the patient should collect 24-hour urine, which will be used to measure the excretion of calcium, phosphate (inherited tubulopathies including Dent disease with present significant proteinuria), oxalate (primary hyperoxaluria), citrate (nephrocalcinosis and hypocitraturia can show medullary sponge kidney) and

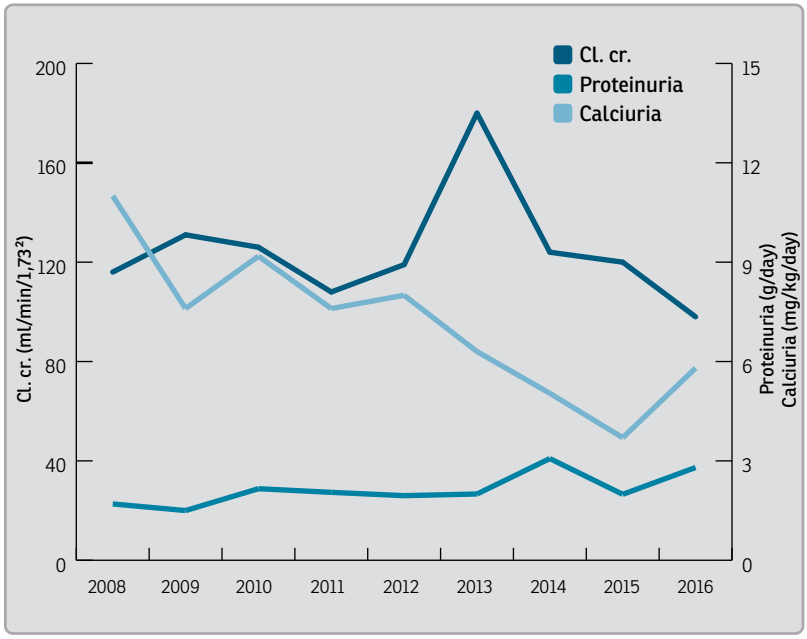

Figure 2: Renal function, proteinuria and calciuria in years 2008–2016

creatinine with renal function assessment (7).

Laboratory findings of the boy showed moderate to severe proteinuria, which was established as mixed, initially selective, then non-selective glomerular proteinuria with tubular proteinuria. Significant tubular proteinuria suggested proximal tubule disorder, as in this part of a healthy tubule low-molecular weight proteins are almost completely absorbed. Hypercalciuria also suggested proximal tubule disorder, which is typical for patients with Dent disease (1-3). The boy had glomerular proteinuria, which was most likely caused by secondary modified Malpighian bodies with the signs of collapsing FSGS and pericapsular fibrosis. These changes were most likely caused by primary tubulointerstitial histopathological changes. Also according to the literature, renal biopsies of patients with Dent disease can show changes, such as interstitial fibrosis, FSGS and/or focal global glomerulosclerosis (FGGS), and also the signs of nephrocalcinosis, which initially was not determined in our patient. Renal biopsy changes in patients with Dent disease are rather non-specific (1,8-10).

The diagnosis is confirmed by molecular-genetic investigations, using sequence analysis method to prove the mutation in the *CLCN5* causal gene (Dent disease 1) or *OCRL* gene (Dent disease 2). In some cases, gene deletion/duplication analysis or multiple-gene panel that includes other genes besides these two is needed (1,2).

In the present case, genetic laboratory of the Faculty of Medicine (mislim) in Ljubljana confirmed the diagnosis with molecular-genetic investigations. Causal gene CLCN5 in hemizygous form was determined. The boy has a pathological substitution c.1909>T(NM_000084.4) that modifies amino acid arginine in stop codon at amino acid position 637 (NP_000075.1:p.Arg637 and NP_001121370.1:p.Arg707Ter). The modification has already been described (11).

Currently two forms of Dent disease are known:

DENT 1 (CLCN5 mutation): The gene causing chloride channel disorder Cl^-/H^+ – transporter (CLC-5) is located on Xp11.22 chromosome and is encoding lysosomal transport protein CLC-5. It is located together with ATP-proton pump on the endosome of proximal tubular cells (2,4,12). In most cases it is clinically manifested as very severe or mild form with hypercalciuria, significant proteinuria (prevalence of low-molecular proteins), nephrocalcinosis and chronic renal disease (1,5). Currently, there are no known data on the number of patients with only mild form of the disease with asymptomatic hypercalciuria and/or proteinuria without progress to chronic renal disease. Some patients develop chronic renal disease with proteinuria without other typical features, such as kidney stones, nephrocalcinosis and

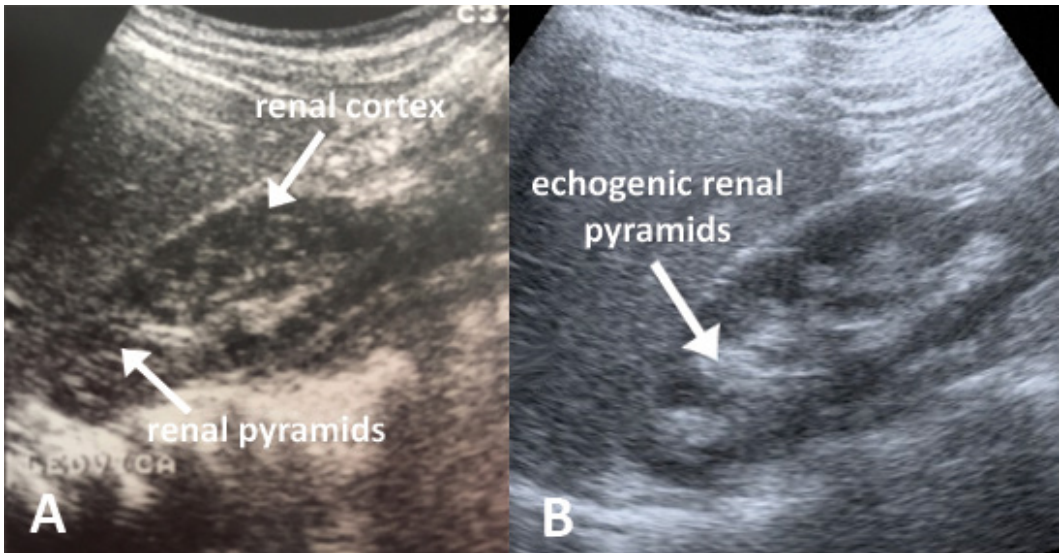

Figure 3: A. Normal sonographic findings in the year 2008 B. Sonographic findings of nephrocalcinosis in the year 2016.

bone disease. Renal biopsy shows FSGS and FGGS (1,8,9).

DENT 2 (OCRL mutation): In this form which occurs in only 15 % of these patients and is much less common than the first one, clinical features are slightly different from "classic" Lowe disease (oculocerebrorenal syndrome), namely: *tubular acidosis* is rare (actually the main sign of Lowe syndrome), the signs of *Fanconi syndrome* (aminoaciduria, glucosuria, renal tubular acidosis) are more typical of Lowe syndrome than of Dent disease type 2; *hypercalciuria, nephrocalcinosis and nephrolithiasis* are typical of Dent disease and rare in Lowe syndrome. Extrarenal manifestations such as mild intellectual disability, hypotonia and cataract are typical (13). The gene causing this form of disease has locus on the X-chromosome Xq25 and is encoding phosphatidylinositol 4,5-biphosphate 5-phosphatase that is involved in actin polymerisation and is located in trans-Golgi network (2,3,14).

The primary goal of the treatment is to decrease hypercalciuria by increased fluid intake, addition of thiazide diuretic and potassium citrate in order to prevent the formation of kidney stones and nephrocalcinosis, and to slow down the progress of chronic renal disease (1-3). Until now no randomized controlled studies on the efficiency of diuretics in children have been performed. Thiazide diuretics in doses over 0.4 mg/kg/day lower calcium excretion in boys with Dent disease by 40 %, however their use is restricted due to the side effects, e.g. hypokalaemia, hypovolemia and cramps. Significant proteinuria in Dent disease can be treated with ACE inhibitors, however their efficiency in preventing further decrease in renal function in children with Dent disease has not been proven (1,10). As the patient had abundant albuminuria with pathohistological changes in Malpighian bodies with the signs of collapsing FSGS, ACE inhibitor was introduced. ACE inhibitors have been proven to have a nephroprotective effect in children with focal segmental glomerulosclerosis (FSGS) (1).

In children with end stage renal disease, substitution treatment with haemodialysis, peritoneal dialysis and kidney transplantation is necessary. In concurrent bone disorders, substitution treatment with vitamin D and phosphate is necessary. In case of poor growth, treatment with growth hormone is described. Diet restriction of calcium intake is not recommended (1-3).

In the present case, ACE inhibitor, potassium citrate and a combination of thiazide diuretic and amiloride were introduced into treatment. The latest bone density measurement along with adequate therapy was normal. The growth is being monitored; currently it is on the lower end of normal.

Conclusion

We present the case of a 3-year-old boy with clinically suspected Dent disease. The disease is a very rare, inherited, X-linked condition that affects the proximal tubules of the kidney, found almost exclusively in males. However, in case of significant proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis it is necessary to think of this disease as well. The diagnosis is confirmed by proving genetic mutations. For a small percentage of patients, the mutation of one or the other gene cannot be proven, which requires the inclusion of other existent genes in the testing. The treatment is based on symptomatic alleviation and prevention of complications.

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