

Dent's disease type 1 in a boy with severe hyperopia and mental dysfunction: a case report

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ABSTRACT

Dent's disease is a rare X-linked recessive proximal tubulopathy. It is typically characterized by low-molecular-weight (LMW) proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, hypophosphatemia, rickets and slowly progressive renal failure. The laboratory and clinical features may occur in various combinations. The early diagnosis of Dent's disease is often problematic because affected children may have mild clinical and biochemical signs, detecting LMW proteinuria

is not available in many laboratories, and genetic results are not clear in all cases. We report on a 12-year-old boy with Dent's disease type 1, severe hyperopia, and psychological dysfunction. To the best of our knowledge, he is the first patient with mutation in *CLCN5* gene and extrarenal symptoms described so far.

Key words: Dent's disease, low-molecular-weight proteinuria, *CLCN5* gene, hypercalciuria, nephrocalcinosis, hyperopia

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INTRODUCTION

Dent's disease is a rare recessive X-linked renal tubular disorder characterized by low-molecular-weight (LMW) proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, hypophosphatemia, rickets and slowly progressive renal failure. Most cases are caused by mutations in the *CLCN5* gene classified as type 1 (OMIM # 300009) whereas mutations in the *OCRL1* gene are responsible for type 2 (OMIM # 300555) of Dent's disease [1]. The true epidemiology of this disorder is unknown but due to its clinical heterogeneity, many cases seem to be under- or misdiagnosed. We describe a case of 12-year boy with subtle expressed features of Dent's disease accompanied by extrarenal symptoms.

Case presentation

A Caucasian boy, a first child of non-consanguineous parents was born prematurely at 35th week of pregnancy with a weight of 2130 g and a length of 50 cm. Family history was uneventful besides urolithiasis in patient's grandfather from paternal side.

The pregnancy was complicated by polyhydramnios, detected shortly before delivery. After birth, congenital pneumonia was diagnosed and treated. Except for severe farsightedness (10 diopters) diagnosed at the age of 4 years, none serious medical problems were observed.

At the age of 6 years an isolated proteinuria was accidentally found. When he was 10 years old, a slightly increased echogenicity of renal pyramids was revealed in ultrasound examination (Fig. 1).

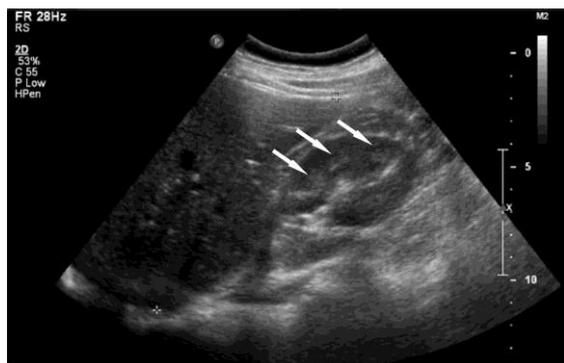


Figure 1. Renal ultrasound of the right kidney in 10-year old patient with Dent's disease. Arrows indicate slightly increased echogenicity of renal pyramids.

Subsequently, a detailed differential diagnostic evaluation of nephrocalcinosis was performed. However, except for persistent proteinuria, no laboratory abnormalities were detected. Either urinary 24-hour excretions of calcium (2.53 mg/kg), oxalate (0.042 mmol/1.73m²

BSA), citrate (2.036 mmol/1.73m² BSA), magnesium (1.85 mg/kg), uric acid (7.86 mg/kg) or serum parameters including calcium (2.53 mmol/l), phosphorus (1.61 mmol/l), uric acid (4 mg/dl) and blood gases (pH 7.41, SBE 1.3 mmol/l, HCO₃⁻ 25.5 mmol/l) were normal. Serum parathormone (PTH) level was in lower normal range (15.3 pg/ml). eGFR was approximately 120 ml/min/1.73 m². Because albumin-content was approximately 15%, a tubular proteinuria was considered. ^{99m}Tc-DMSA scan revealed an inhomogeneous distribution of radiotracer in renal parenchyma, which was lower in the upper-medial part of the right kidney. That suggested a renal scarring as a cause of proteinuria. Because a subsequent follow-up within a year revealed slightly increased 24-h urinary calcium excretion, 4.68 and 4.95 mg/kg, a suspicion of Dent's disease was made. The result of genetic testing revealed a hemizygous double nucleotide deletion in exon 4 of the *CLCN5* gene confirming the diagnosis of Dent's disease type 1. The treatment with thiazides and diet with salt restriction was started, lowering daily urinary calcium excretion under 4 mg/kg. During 2-year follow-up the 24-hour urinary protein excretion ranged between 370 and 670 mg and no deterioration of renal function was noticed.

The patient's physical growth was normal (body weight and height at the level of 86 and 28 centiles, respectively). Psychological evaluation was necessary due to his educational and behavioral problems. The results showed impaired cognitive function, emotional immaturity, strong nervous tension, high neurotic anxiety, emotional hypersensitivity, low self-esteem, sense of security and self-criticism.

DISCUSSION

Dent's disease is rare recessive X-linked renal tubular disorder manifesting by proximal tubular dysfunction of different grades, nephrolithiasis, nephrocalcinosis, rickets and slowly progressive renal failure. Its precise prevalence is unknown and approximately 250 affected families were reported worldwide. In the past, several phenotypic variants of Dent's disease were independently described and named as separate disorders, including X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets and familial idiopathic LMW proteinuria with hypercalciuria in Japanese patients [2].

Mutations in the *CLCN5* gene encoding the electrogenic chloride/proton exchanger CIC-5 participating in the receptor-mediated endocytosis in the proximal tubule are a causative factor for Dent's disease of type 1. Large number of different mutations in this gene was identified, until now, but no clear genotype-phenotype correlation was found.

Dent's disease of type 1 is characterized by symptoms exclusively related to proximal tubular dysfunction. Dent's disease of type 2 is thought to be a mild variant of oculocerebrorenal syndrome (Lowe syndrome) because both conditions are caused by mutation in the *OCRL1* gene and therefore, the former is manifested sometimes with extrarenal features, including mild ocular involvement, mild intellectual disability, muscle hypotonia, umbilical hernia or short stature [2,3]. In our patient, extra-renal symptoms, including severe hyperopia and mental problems are quite unusual and, to the best of our knowledge, have never been reported before. Currently, it remains unclear whether it is just a coincidence or a true syndromic association. Therefore, functional studies seem to be required to determine the exact effect of mutation in *CLCN5* gene. On the other hand, extra-renal symptoms in our patient might be the result of coexistence of mutations in the *OCRL1* and the *CLCN5* genes what was recently reported in the literature [4]. Unfortunately, we were not able to proof *OCRL1* mutation in our patient so far. We will try to complete the genetic evaluation in the future.

Approximately, one-fourth of the patients with Dent's disease do not have mutations in any of the above-mentioned genes. Therefore, other candidate genes are postulated such as *CLCN4*, *CFL1*, *SLC9A6* and *TMEM27* [2].

Due to the mode of inheritance Dent's disease affects primarily males. Female carriers remain predominantly asymptomatic, although they may have mild proteinuria and/or hypercalciuria [1, 2]. It was not a case in our patient's mother.

The clinical features of Dent's disease are often subtle with the majority of patients being asymptomatic during infancy and early childhood. Initial symptoms may be variable and non-specific, including polyuria, proteinuria, microscopic hematuria or renal colic due to urolithiasis. Therefore, some of the patients similar to our one may be diagnosed accidentally. Growth retardation may be present [2], but that was not observed in our patient.

Proteinuria resulted from impaired reabsorption of proteins in proximal tubules is a typical and constant feature of Dent's disease and consists mainly of different LMW-proteins, including alpha-1- and beta-2-microglobulin, cystatin C, lysozyme, retinol-binding protein (RBP), vitamin-D-binding protein and trace amounts of albumins [2]. Unfortunately, as in our study, an evaluation of LMW-proteinuria may be problematic due to laboratory limitations.

Urinary protein excretion in patients with Dent's disease is usually moderate and only in rare cases of coexisting focal segmental glomerulosclerosis reaches the nephrotic range [5].

Hypercalciuria of different severity affects

approximately 90% of patients. Urinary calcium excretion is usually higher in children than in adults, because calciuria tapers with decreasing renal function [2]. However, it may be initially absent as in our patient and occur later in a course of the disease. Therefore, in doubtful cases, it is reasonable to assess urinary calcium excretion repeatedly. Interestingly, serum PTH level as in our patient is frequently low, probably due to renal loss of this hormone [2].

Nephrocalcinosis is an important feature of Dent's disease affecting approximately 75% of patients [2]. It may serve as a cue leading to final diagnosis. Nephrolithiasis is observed markedly less commonly, and stones usually consist of calcium phosphate or calcium oxalate [2]. Hypercalciuria is thought to be a main etiological factor of nephrocalcinosis and urolithiasis because as in our patient urinary oxalate and citrate, excretion is usually normal.

The increased activation of PTH receptors on the apical membrane of the proximal tubule by excreted PTH may cause urinary phosphate loss, hypophosphatemia and rickets in a minority of patients [2, 6].

Patients with Dent's disease show a poor accumulation of ^{99m}Tc-DMSA in renal parenchyma and rapid excretion of radiotracer due to proximal tubular endocytic dysfunction [2,7]. That could be a reason of inhomogeneous distribution of radiotracer in DMSA scan of our patient leading us to false diagnosis of renal scarring and post-inflammatory nephropathy.

In most children with Dent's disease, renal function is normal, but unfortunately, it declines during adulthood. The pathomechanism of this process is still unclear. 30 to 80% of affected patients progress to end stage renal failure in the third to fifth decade of life [2].

Some patients develop recurrent episodes of nocturnal blindness, probably due to renal losses of RBP. They are responsive to vitamin A therapy [8].

Currently, there is no clear strategy for the management of patients with Dent's disease and recommended treatment is mostly supportive. Thiazide diuretics and dietary salt restriction are used to reduce calciuria and to prevent the occurrence of nephrocalcinosis and nephrolithiasis. This treatment seemed to be effective in our patient. ACE inhibitors may be useful to reduce glomerular component of proteinuria [9]. In recent animal studies a high-citrate diet seems to delay the progression of renal failure [10].

CONCLUSIONS

The presented case confirms difficulties in early diagnosis of Dent's disease. This rare disorder should be considered in differential diagnosis of

unexplained proteinuria, accompanied by hypercalciuria and nephrocalcinosis/uroolithiasis. In doubtful cases, the genetic testing may be necessary.

If extrarenal features observed in our patient may be a new manifestation of Dent's disease remains hypothetical.

Conflicts of interest

The authors declare that they have not any conflicts of interest.

Financial disclosure

None.

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