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Exceptional Case

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Two brothers with identical variants of the *CLCN5* gene—one developing Dent's disease

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Abstract

Dent's disease is characterized by manifestations of proximal tubule dysfunction including hypercalciuria, kidney stones, proteinuria, rickets and progressively declining kidney function. The diagnosis is based on the presence of low-molecular-weight proteinuria, hypercalciuria and at least one of the following: nephrocalcinosis, kidney stones, haematuria, hypophosphataemia or renal insufficiency. Dent's disease is a hereditary condition that is caused by variants in the *CLCN5* gene or the *OCRL1* gene and affects only males. Herein, we report on two brothers who were found to have a previously reported disease-causing variant in the *CLCN5* gene. One sibling had nephrocalcinosis, proteinuria and hypercalciuria, whereas the other sibling was asymptomatic and had normal laboratory findings.

Key words: calcification, chronic renal failure, gene polymorphism, nephrolithiasis, proteinuria

Introduction

Dent's disease, first described in 1964 [1], comprises a group of familial tubular syndromes [2] known to affect approximately 250 families in the world [3]. They often share a common aetiology consisting of variants in the *CLCN5* gene, which is located on chromosome Xp11.22 and encodes a lysosomal transport protein, ClC-5, a chloride channel predominantly expressed in the kidney [4]. The variant either decreases or abolishes the function of the chloride channel [5]. Dent's disease Type 2 is caused by variants in the *OCRL1* gene, which is located on chromosome Xq25 and encodes a phosphatase. To date, Dent's disease Type 2 is known to affect approximately 20 patients [6]. Dent's disease Type 1 and Dent's disease Type 2 have different aetiologies but show a similar kidney phenotype. However, patients with variants in the *OCRL1* gene may show extra-renal manifestations such as mild intellectual impairment, hypotonia and cataract. Variants in *OCRL* may also lead to a more severe phenotype with congenital cataract termed Lowe syndrome [7]. Variants in other genes may, in some patients, cause Dent's disease [8].

Dent's disease is characterized by manifestations of proximal tubule dysfunction including hypercalciuria, kidney stones, proteinuria and rickets. In 30–80% of patients, the disease progresses to end-stage renal disease (ESRD) between the third and fifth decades of life [9].

Dent's disease is inherited in an X-linked recessive manner such that it affects only males. Female carriers are not significantly

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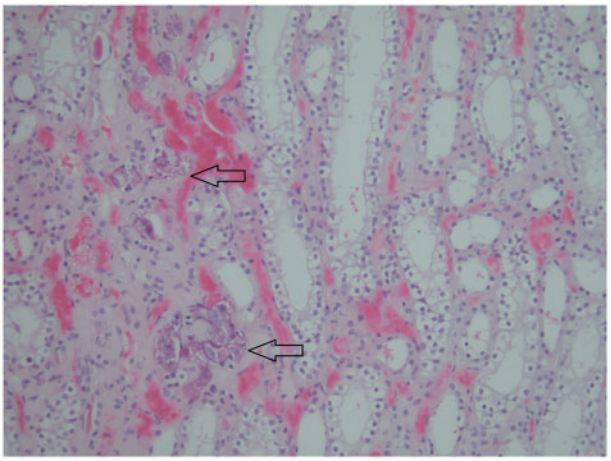

Fig. 1. Renal medulla with calcifications (arrows) in the medullary interstitium and in the thin loops of Henle. Haematoxylin and eosin stain, 200×.

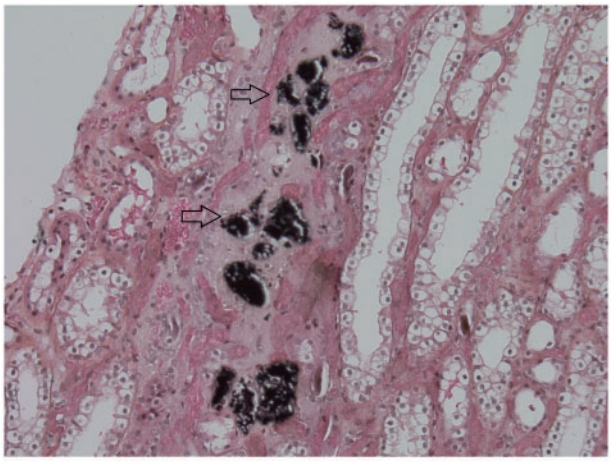

Fig. 2. Renal medulla with calcifications. von Kossa stain, 200×.

affected [10]. The disease is caused by variants in the *CLCN5* gene or the *OCRL1* gene. Treatment is supportive, with a focus on preventing nephrolithiasis by increasing fluid intake. Thiazide diuretics may decrease hypercalciuria. However, thiazide administration may be complicated by sodium wasting and excessive diuresis.

Case report

A 23-year-old Caucasian male was referred from his general practitioner (GP) to our nephrology outpatient clinic due to proteinuria (2 g/day) and elevated plasma creatinine (109 μmol/L). At referral, he was asymptomatic. He was known to have attention-deficit/hyperactive disorder and was being treated with methylphenidate. A renal biopsy was performed. Light microscopic examination of medullary tissue showed medullary interstitial fibrosis, tubular atrophy and calcinosis in medullary tubules (Figures 1 and 2). Immunofluorescence and electron microscopy of glomeruli did not reveal any specific changes; in particular, there were no signs of segmental sclerosis. Fibrosis was observed in the interstitium.

Physical examination was unremarkable. The patient was normotensive (125/79 mmHg). Laboratory findings showed elevated plasma creatinine (123 μmol/L), normal plasma glucose (5.7 mmol/L), elevated haemoglobin (11.3 mmol/L), slightly elevated ionized calcium (1.35 mmol/L) and low parathyroid hormone (1.2 pmol/L). Urine dipstick testing showed ++protein, ++blood and ++glucose. Further investigation included 24-h urine collection, which revealed proteinuria of 1.74 g/day and hypercalciuria of 10.5 mmol/day, as well as a low amount of citrate in the urine (0.34 mmol/day). On examination 2 months later, his blood pressure (155/85 mmHg) and plasma creatinine (154 μmol/L) had increased, and treatment with ramipril (2.5 mg daily) was initiated. After 3 months, he was hospitalized due to abdominal pain with fluctuating intensity. A computed tomography scan showed calcinosis and small kidney stones, 4 mm in diameter. In sonographic images, the kidneys appeared slightly small. The right kidney had a length of 10.3 cm, and the left kidney had a length of 9.9 cm. There were no signs of urinary tract obstruction. The patient was prescribed thiazide with potassium chloride (2.5 mg daily) to decrease hypercalciuria. Prior to treatment his plasma electrolytes were normal: potassium 3.8 mmol/L, phosphate 0.67 mmol/L, ionized calcium 1.29 mmol/L and plasma creatinine 157 μmol/L.

After 2 months, his GP contacted us because the patient had severe hypokalaemia (2.5 mmol/L) despite administration of potassium (1500 mg daily) for a few days. It was recommended that the GP discontinued the administration of thiazide with potassium chloride and prescribed potassium as well as increased the dose of ramipril to 10 mg/day.

Proteinuria, hypercalciuria, glycosuria, nephrocalcinosis and severe hypokalaemia following administration of thiazide in combination with elevated plasma creatinine are signs of proximal tubule dysfunction. Urine protein electrophoresis was performed to confirm the diagnosis, and the result showed elevated β2-microglobulin (80× normal range), urine albumin (10× normal range) and glycosuria. Sanger sequencing of the *CLCN5* and *OCRL* genes identified the variant *CLCN5* (c.473G>A, p.Gly158Asp). This variant has previously been reported in three family members affected by Dent's disease in a German family [11]. No variant form of the *OCRL* gene was identified.

The patient's brother had no symptoms, but nonetheless underwent medical evaluation. His blood pressure was 145/85 mmHg. Laboratory findings were all within normal range: plasma creatinine 91 μmol/L, potassium 4.0 mmol/L, phosphate 0.97 mmol/L and calcium 1.22 mmol/L. The 24-h urine collection presented normal excretion of calcium, citrate and oxalate. A computed tomography scan showed neither concretions nor nephrocalcinosis. Predictive genetic testing identified the same *CLCN5* variant in the brother. He will be followed up in our nephrological outpatient clinic to monitor future symptoms, which could progress to Dent's disease.

Discussion

The variant of the *CLCN5* gene had previously been reported as disease-causing. Our patient and his brother had this variant and did not have any extra-renal manifestations. Before the genetic analysis was performed, different causes of proximal renal tubular acidosis with Fanconi syndrome were considered; these causes can be separated into genetic and acquired disorders. The acquired disorders may include amyloidosis, multiple myeloma, paroxysmal nocturnal haemoglobinuria and administration of drugs, for instance, antiviral therapy [12]. The patient did not have signs of any of these diseases and had not taken any drugs other than the methylphenidate prescribed by his GP.

Dent's disease has been previously reported to be present already in childhood with asymptomatic proteinuria [13, 14]. The fully expressed clinical disease has been reported in a 3-

year old with evident nephrolithiasis progressing to ESRD at the age of 40 years [15]. Reinhart *et al.* [16] have reported different clinical presentations of patients with *CLCN5* variants, raising the possibility that Dent's disease may occur more commonly, in less overt forms and possibly without an apparent family history. In this case, we were suspicious of the diagnosis when the patient developed severe hypokalaemia following treatment with thiazide. In retrospect, attention should have been brought to proximal tubulopathy earlier as the patient was a young male with glycosuria but normal serum glucose combined with symptoms of kidney stones and signs of nephrocalcinosis.

Patients with Dent's disease and glomerular abnormalities on renal biopsy usually have focal global glomerulosclerosis. The tubulointerstitial findings are variable and range from normal to interstitial fibrosis or tubular atrophy [17]. Moulin *et al.* have studied eight renal biopsies from patients with Dent's disease showing focal hyaline casts, sometimes calcified, which can be identified at all stages of the disease [18]. In our case, kidney biopsy 3 years prior to diagnosis showed interstitial calcinosis in medullary tubules, which may be an early sign of nephrocalcinosis. The patient had no symptoms at the time of renal biopsy, but proteinuria and slightly elevated plasma creatinine (109 μmol/L). At this point we had not investigated the proteinuria for β2-microglobulin as it is not routinely performed. If it had showed low molecular weight proteinuria, the hallmark of Dent's disease, we could have diagnosed the patient earlier.

Although Dent's disease is now well reported and its aetiology is known, there is still no clear strategy for managing the disease [19]. No randomized controlled trials have been performed. The primary goals, however, are to decrease hypercalciuria, to prevent kidney stone formation and nephrocalcinosis, and to delay progression to ESRD. Thiazide diuretics have been used for many years to control hypercalciuria and the recurrence of nephrolithiasis. Thiazide diuretics have a dual effect on calcium clearance not produced by most other natriuretic drugs. First, on initial administration, thiazide diuretics do not enhance calcium excretion in proportion to sodium excretion. Second, on sustained administration, thiazide diuretics cause a persistent reduction in calcium excretion by acting on the distal renal tubule, where *CLCN5* is not expressed, enhancing calcium reabsorption [20]. Patients are advised to increase their fluid intake and avoid vitamin D, as it increases calcium excretion and thereby stone formation. Cebotaru *et al.* [21] fed a knockout mouse model of Dent's disease on a high-citrate diet, which preserved kidney function. Based on that study, Cebotaru *et al.* recommended long-term control of hypercalciuria as an important factor. To our knowledge, these findings of a high-citrate diet protecting the kidney have not been translated into human patients yet.

In conclusion, we present a case report on Dent's disease involving two brothers with an identical *CLCN5* variant, but due to incomplete penetrance, only one brother has developed symptoms so far. Although Dent's disease is a very rare disorder, it should be kept in mind in diagnosing male patients who present with nephrocalcinosis, proteinuria and hypercalciuria with development of severe hypocalcaemia on thiazide treatment.

Conflict of interest statement

None declared.

References

1. Dent CE, Friedman M. Hypercalcuric rickets associated with renal tubular damage. *Arch Dis Child* 1964; 39: 240–249
2. Norden AG, Scheinman SJ, Deschodt-Lanckman MM *et al.* Tubular proteinuria defined by a study of dent's (CLCN5 mutation) and other tubular diseases. *Kidney Int* 2000; 57: 240–249
3. Devuyst O, Thakker RV. Dent's disease. *Orphanet J Rare Dis* 2010; 5: 28
4. Fisher SE, Black GC, Lloyd SE *et al.* Isolation and partial characterization of a chloride channel gene which is expressed in kidney and is a candidate for Dent's disease (an X-linked hereditary nephrolithiasis). *Hum Mol Genet* 1994; 3: 2053–2059
5. Gunther W, Luchow A, Cluzeaud F *et al.* ClC-5, the chloride channel mutated in dent's disease, colocalizes with the proton pump in endocytotically active kidney cells. *Proc Natl Acad Sci USA* 1998; 95: 8075–8080
6. Solano A, Lew SQ, Ing TS. Dent-wrong disease and other rare causes of the Fanconi syndrome. *Clin Kidney J* 2014; 7: 344–347
7. Sharma S, Skowronek A, Erdmann KS. The role of the Lowe syndrome protein OCRL in the endocytic pathway. *Biol Chem* 2015; 396: 1293–1300
8. Hoopes RR, Jr, Raja KM, Koich A *et al.* Evidence for genetic heterogeneity in Dent's disease. *Kidney Int* 2004; 65: 1615–1620
9. Wrong OM, Norden AG, Feest TG. Dent's disease; a familial proximal renal tubular syndrome with low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease, progressive renal failure and a marked male predominance. *QJM* 1994; 87: 473–493
10. Lieske JC, Milliner DS, Beara-Lasic L *et al.* Dent disease. In: Pagon RA, Adam MP, Ardinger HH *et al.* (eds). *Gene Reviews(R)*. Seattle, WA: University of Washington, 1993, NBK99494 [bookaccession]
11. Ludwig M, Doroszewicz J, Seyberth HW *et al.* Functional evaluation of Dent's disease-causing mutations: Implications for ClC-5 channel trafficking and internalization. *Hum Genet* 2005; 117: 228–237
12. Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. *Nephrol Dial Transplant* 2012; 27: 4273–4287
13. Copelovitch L, Nash MA, Kaplan BS. Hypothesis: Dent disease is an under-recognized cause of focal glomerulosclerosis. *Clin J Am Soc Nephrol* 2007; 2: 914–918
14. Hodgin JB, Corey HE, Kaplan BS *et al.* Dent disease presenting as partial Fanconi syndrome and hypercalciuria. *Kidney Int* 2008; 73: 1320–1323
15. Frymoyer PA, Scheinman SJ, Dunham PB. *et al.* X-linked recessive nephrolithiasis with renal failure. *N Engl J Med* 1991; 325: 681–686
16. Reinhart SC, Norden AG, Lapsley M *et al.* Characterization of carrier females and affected males with X-linked recessive nephrolithiasis. *J Am Soc Nephrol* 1995; 5: 1451–1461
17. Murakami T, Kawakami H. The clinical significance of asymptomatic low molecular weight proteinuria detected on routine screening of children in Japan: a survey of 53 patients. *Clin Nephrol* 1990; 33: 12–19
18. Moulin P, Igarashi T, Van Der Smissen P *et al.* Altered polarity and expression of H+-ATPase without ultrastructural changes in kidneys of Dent's disease patients. *Kidney Int* 2003; 63: 1285–1295
19. Burgess HK, Jayawardene SA, Velasco N. Dent's disease: can we slow its progression? *Nephrol Dial Transplant* 2001; 16: 1512–1513
20. Costanzo LS, Weiner IM. On the hypocalciuric action of chlorothiazide. *J Clin Invest* 1974; 54: 628–637
21. Cebotaru V, Kaul S, Devuyst O *et al.* High citrate diet delays progression of renal insufficiency in the ClC-5 knockout mouse model of Dent's disease. *Kidney Int* 2005; 68: 642–652

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