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Teaching Point
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A young man presenting with recurrent nephrolithiasis

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Introduction

We present a patient with recurrent nephrolithiasis, nephrocalcinosis, renal impairment, heavy proteinuria and multiple renal cysts. We focused on the differential diagnosis of nephrocalcinosis, which led us to the rare entity of Dent's disease. This diagnosis was confirmed by molecular analysis, revealing a mutation in the CLCN5 gene.

Case

A male patient, born in 1990, first presented with a kidney stone when he was 10 years old, but the stone had passed spontaneously, and no further testing was done at that time. At the age of 20, he presented with a second episode of renal colic. Proteinuria and microscopic haematuria were also noticed, for which he was referred to a nephrologist.

On examination, he was a lean young man with normal height and stature. Height was 175 cm, and weight was 59 kg. Systemic examination was unremarkable. Blood pressure was 107/74 mmHg.

Laboratory examination showed an elevated serum creatinine of 130 μmol/L (1.44 mg/dL) (eGFR 62 mL/min/1.73 m^2). Serum alkaline phosphatase level was 122 U/L with elevated bone fraction of alkaline phosphatase. Other blood tests were normal. Twenty-four-hour urine collection showed proteinuria of 2.981 g/day consisting mainly of low-molecular-weight proteins. Calciuria was 8.3 mmol/day (334 mg/day) or 5.7 mg/kg/day (normal <4). Urine sediment analysis was normal (Table 1).

Ultrasonography, CT scan and MRI revealed normal kidney size and contour but bilateral multiple cysts. The cysts were mainly localized in the cortex, and they had a benign simple appearance. Furthermore, bilateral nephrolithiasis and intraparenchymal calcification consistent with nephrocalcinosis were seen (Figures 1 and 2).

Renal biopsy had been performed in another centre and had shown normal light microscopy, normal electron microscopy, and negative immunofluorescence.

After the acute renal colic, transurethral stone extraction was performed. Stone analysis showed a stone consisting of calcium phosphate and calcium oxalate.

Family history was negative for renal disease or renal colic. The patient had no siblings. The parents underwent a renal ultrasound examination: both had normal morphology of their kidneys without cysts, but one asymptomatic nephrolithiasis was found in the father.

Discussion

Our differential diagnosis included disorders resulting in nephrocalcinosis. This term is used to describe the deposition of calcium in the renal parenchyma and tubules. It is caused by an increase in the urinary excretion of calcium, phosphate and/or oxalate. Hypocitraturia also may contribute. Underlying conditions can be categorized into those that cause hypercalciuria with hypercalcaemia, hypercalciuria without hypercalcaemia, hyperphosphaturia, or hyperoxaluria (Table 2).

Our patient presented with nephrocalcinosis in the presence of hypercalciuria. He had no hypercalcaemia, hyperparathyroidism, hyperphosphaturia or hyperoxaluria, which narrows our differential diagnosis down to (inherited) tubulopathies, chronic hypokalaemia, medullary sponge kidney or sarcoidosis. The normal serum bicarbonate practically rules out RTA type 1, and the absence of hypokalaemia or alkalosis makes Bartter's syndrome very unlikely. Since there is no hypocalcaemia or hypomagnesaemia, other inherited tubulopathies such as autosomal dominant hypocalcaemia or hypomagnesaemia, and hypercalciuric nephrocalcinosis can also be excluded. Moreover neither of these aforementioned disorders are associated with heavy low-molecular-weight proteinuria. Sarcoidosis can also result in hypercalciuria and nephrocalcinosis, sometimes without overt hypercalcaemia, but since the biopsy did not show granulomatous interstitial nephritis or glomerular disease, the proteinuria could not be explained. Patients with medullary sponge kidney present with nephrocalcinosis and renal cysts, bringing us closer to this patient's situation. But in the medullary sponge kidney, cysts would be confined to the renal medulla which is not the case here,

Table 1. Laboratory examinations

Serum/blood concentration	Normal value	24-h urine collection	Normal value
BUN	6.1 mmol/L (3.0–6.5)	Volume	2960 mL
Creatinine	130 μmol/L (50–110)	Sodium	178 mmol/day (40–220)
MDRD	62 mL/min/1.73 m²	Potassium	72 mmol/day (25–125)
Sodium	142 mmol/L (137–145)	Glucose	Below detection limit
Potassium	3.7 mmol/L (3.5–5.0)	Creatinine	12.8 mmol/day (8.8–17.6)
Chloride	103 mmol/L (98–107)	Calcium	8.3 mmol/day (<6.2)
Bicarbonate + CO_2	26 mmol/L (23–30)	Inorganic phosphate	42 mmol/day (12.9–42.0)
Calcium	2.42 mmol/L (2.20–2.58)	Magnesium	3.2 mmol/day (3.0–5.0)
Inorganic phosphate	0.97 mmol/L (0.80–1.60)	Oxalic acid	310 μmol/day (110–440)
Magnesium	0.94 mmol/L (0.80–1.20)	Citric acid	3.77 mmol/day (2.12–6.26)
Uric acid	240 μmol/L (120–420)	Total protein	2.981 g/day (<0.15)
Albumin	52 g/L (40–60)	Protein electrophoresis	Mixed tubular/glomerular
Total protein	76 g/L (60–80)	Immunofixation	proteinuria (mainly LMW proteins)
Alkaline	122 U/L (36–95)		Negative
Phosphatase	2.2 pmol/L (1.2–5.8)		
Intact PTH	62 nmol/L (45–90)	Urine spot test	
25-OH vitamin D		Cystine qualitative test	Negative
		pH	7.0

nor would we expect heavy proteinuria or diminished renal function in this disease.

Hereditary renal cystic diseases were also considered. The parents did not have renal cysts, ruling out autosomal dominant inheritance. Moreover, none of the genetic disorders typically presenting with renal cysts is associated with either heavy proteinuria or hypercalciuria.

There is only one disease that perfectly matches with our patient's abnormalities, which is Dent's disease. The term Dent's disease is used to describe a phenotype characterized by X-linked inheritance, low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis and progressive renal failure [1]. It is a hereditary tubulopathy, in the large majority of cases caused by a mutation in the CLCN5 gene. Multiple renal cysts have been reported in Dent's disease [1], although they are not commonly used as a diagnostic feature.

In this patient, the diagnosis was confirmed by molecular analysis, revealing a mutation in the CLCN5 gene (c.815A>G). The same mutation was found in the mother. This mutation has been reported before [2].

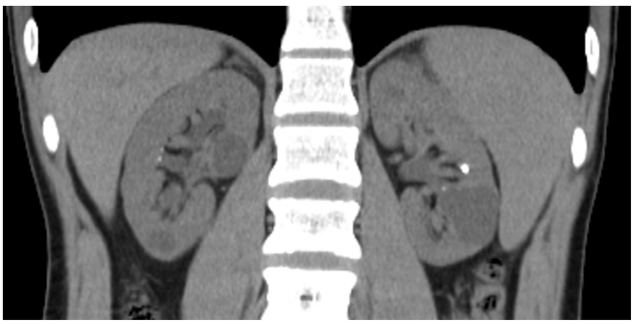

Fig. 1. CT scan without intravenous contrast: this image shows intraparenchymal calcification in the right kidney consistent with nephrocalcinosis, and nephrolithiasis in a mid-pole calyx of the left kidney. Bilateral renal cysts are present.

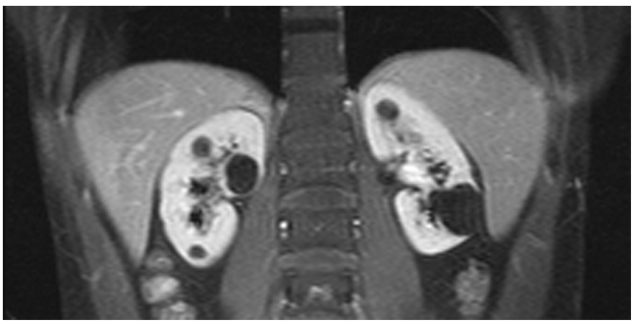

Fig. 2. MRI scan confirms bilateral multiple cysts: at least six cysts in the left and four in the right kidney. The cysts are localized in the renal parenchyma, mainly in the cortex, and they have a benign simple appearance (Bosniak category I). The largest cyst has a diameter of 3 cm.

Dent's disease

The term Dent's disease, first introduced in 1990 [1], identifies a group of X-linked renal disorders characterized by low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis, and progressive renal failure. The disease also may be associated with aminoaciduria, phosphaturia, glycosuria, kaliuresis, uricosuria, and impaired urinary acidification, and is complicated by rickets or osteomalacia in some patients. Thus, Dent's disease may be considered a form of the renal Fanconi syndrome [1]. In the majority of cases, the disease is caused by a mutation in the CLCN5 gene, which encodes a voltage-gated chloride transporter expressed mainly in the renal tubular cells [3]. A similar renal phenotype is seen in patients with Lowe syndrome, due to a mutation in the ORCL1 gene, but these patients typically have congenital cataracts, mental retardation and renal tubular acidosis which are absent in classical Dent's disease. This entity has been designated as Dent's disease 2 [4]. Further genetic heterogeneity is assumed to exist, since there are patients with the distinctive phenotype of Dent's disease without mutation in either of these genes [2].

The disease usually presents in childhood or early adult life. Symptomatic disease is almost exclusively seen in males, with inheritance being X-linked recessive, although carrier females may present some manifestations of Dent's

Table 2. Differential diagnosis of nephrocalcinosis

Hypercalciuria with hypercalcaemia[a]	**Hypercalciuria without hypercalcaemia**
Primary hyperparathyroidism	Type 1 (distal) renal tubular acidosis (inherited or secondary)
Sarcoidosis (or other granulomatous disease)	Medullary sponge kidney
Vitamin D therapy	Loop diuretics
Milk alkali syndrome	Nephrocalcinosis in premature infants
	Chronic hypokalaemia
	Inherited tubulopathies
	Bartter's syndrome
	Hypomagnesaemic hypercalciuric nephrocalcinosis
	Autosomal dominant hypocalcaemia
	Dent's disease
	Lowe syndrome
	Idiopathic hypercalciuria
Hyperphosphaturia	**Hyperoxaluria**
Inherited tubulopathies	Primary hyperoxaluria
X-linked hypophosphataemic rickets	Secondary hyperoxaluria
Autosomal dominant hypophosphataemic rickets	Fat malabsorption
Hereditary hypophosphataemic rickets with hypercalciuria	Excessive intake of foods rich in oxalic acid
Dent's disease	Ingestion of ethylene glycol or methoxyflurane
Lowe syndrome	
Acquired renal phosphate wasting	
Tumour-induced osteomalacia	
Renal transplant	
Acute phosphate nephropathy	
Oral sodium phosphate bowel preparations	
Tumour lysis syndrome	

[a]Although a minority of patients may be intermittently or persistently normocalcaemic.

disease [5]. Many affected men progress to end-stage renal failure between the third and fifth decades of life.

The pathophysiology of Dent's disease is still incompletely understood. Mutations in the CLCN5 gene lead to inactive CLC-5 chloride channel function. In the human kidney, CLC-5 is primarily expressed in proximal tubular cells, in cortical collecting duct intercalated cells and also in the thick ascending limb of Henle's loop [6]. In proximal cells, CLC-5 is predominantly located in the subapical endosomes, which are involved in the endocytotic reabsorption of low-molecular-weight (LMW) proteins that have passed the glomerular filter. CLC-5 allows for acidification of the endosomes; dysfunctional CLC-5 results in impaired acidification and failure to process adsorbed proteins. This may also lead to impaired recycling of endosomal membrane back to the apical surface [7]. This explains the LMW proteinuria in patients with Dent's disease. However, the mechanism by which CLCN5 mutations result in hypercalciuria remains to be elucidated. Also, the cause of renal function impairment in Dent's disease is not completely understood. Although renal calcification was first suspected to be involved in the decline in renal function, hypercalciuria and nephrolithiasis have been shown to be of poor predictive value in identifying individuals at risk for developing renal insufficiency [8].

To date, >85 different nonsense or missense mutations, insertions, or deletions in the CLCN5 gene have been reported in the literature, meaning that the spectrum of CLCN5 mutations is highly varied [2]. There is no correlation found between the nature of the mutation and the presence of particular clinical features or the overall severity of the disease.

Treatment measures are mostly supportive. Although it is unknown to what extent hypercalciuria is responsible for the renal failure in Dent's disease, it is the major factor promoting nephrolithiasis. Therefore, an attempt to reduce calcium excretion is reasonable. This can be done by restricting dietary sodium intake (since sodium excretion promotes calcium excretion) and by administering a thiazide diuretic. Thiazides reduce the rate of calcium stone recurrence in patients with idiopathic hypercalciuria [9], and a similar correction of hypercalciuria has been shown in patients with Dent's disease [10]. However, because severe hypokalaemia can be seen in these patients using only moderate doses of thiazide diuretics [11], starting with small doses and regular electrolyte controls is mandatory. In a mouse model of Dent's disease, a diet high in citrate showed a delayed progression of renal failure, possibly by enhancing calcium solubility in the urine [12].

Early diagnosis could theoretically help to prevent the progression to end-stage renal disease, but the clinical diagnosis of Dent's disease is often difficult since patients may have only mild clinical and biochemical signs, and the X-linked inheritance is not always obvious. Carrier mothers or daughters of an affected male may not present LMW proteinuria [13]. CLCN5 mutations are demonstrated in >85% of patients, when the clinical diagnosis of Dent's disease is made based on the concurrence of LMW proteinuria, hypercalciuria and nephrocalcinosis [2]. Besides displaying this classic symptomatic triad, our patient presented

with multiple renal cysts on medical imaging techniques. Multiple renal cysts have been reported in Dent's disease [1], although they are not commonly used as a diagnostic feature.

Conclusion

In summary, this young man presented with renal impairment, low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis and multiple renal cysts. Furthermore, the persistently elevated serum alkaline phosphatase level suggested abnormal bone metabolism. This phenotype was consistent with Dent's disease. The diagnosis was confirmed by molecular analysis, revealing a mutation in the CLCN5 gene. Besides displaying the classical diagnostic criteria of Dent's disease, our patient presented with multiple renal cysts. Although multiple renal cysts have been reported in Dent's disease, they are not commonly used as a diagnostic feature. Other observations are needed to explore the possible correlation between the nature of the mutation and the cystic phenotype of Dent's disease.

Teaching points

(1) Nephrocalcinosis indicates an increase in the urinary excretion of calcium, phosphate and/or oxalate. Underlying conditions can be categorized into those that cause hypercalciuria with hypercalcaemia, hypercalciuria without hypercalcaemia, hyperphosphaturia, or hyperoxaluria.

(2) Dent's disease is a hereditary tubulopathy, in the large majority of cases caused by a mutation in the CLCN5 gene. It is characterized by X-linked inheritance, low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis and progressive renal failure.

(3) Dent's disease can present with multiple renal cysts, and may be considered in the differential diagnosis of cystic renal disease.

Conflict of interest statement. None declared.

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