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Exceptional Case

EXCEPTIONAL CASE

Hemizygous loss of function mutations in *CLCN5* causing end-stage kidney disease without Dent disease phenotype

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ABSTRACT

Dent disease type 1 is suspected in the presence of a complete phenotype of low molecular weight (LMW) proteinuria, hypercalciuria and at least one of the following: nephrocalcinosis, nephrolithiasis, haematuria, hypophosphatemia or chronic kidney disease (CKD). We present two brothers who presented with CKD alone. In the absence of typical clinical features, further assessment of LMW proteinuria and hypercalciuria was not undertaken. Whole-genome sequencing revealed hemizygous loss of function mutations in chloride voltage-gated channel 5 (*CLCN5*) consistent with Dent disease. Dent disease should, therefore, be considered in patients with an incomplete phenotype, including unexplained CKD alone.

Keywords: chronic kidney disease, *CLCN5*, Dent disease, nephrocalcinosis, nephrolithiasis

INTRODUCTION

Dent disease type 1 is an X-linked disorder predominantly affecting males with causal mutations in chloride voltage-gated channel 5 (*CLCN5*), resulting in proximal kidney tubule dysfunction. Prior to routine molecular genetic diagnoses, Dent disease was diagnosed in patients as a syndrome with a complete phenotype. It is traditionally suspected in the presence of high levels of low molecular weight (LMW) proteinuria, hypercalciuria and at least one of the following: nephrocalcinosis, nephrolithiasis, haematuria, hypophosphatemia or chronic kidney disease (CKD) [1].

CASE REPORT SIBLING 1

A 23-year-old male presented with end-stage kidney disease (ESKD) (serum creatinine 1246 μmol/L) (see Table 1). Urinalysis showed +1 blood and +3 protein. Ultrasound revealed bilateral small kidneys with multiple cysts but no nephrocalcinosis or nephrolithiasis. He commenced continuous ambulatory peritoneal dialysis (CAPD) followed by a kidney transplant. He complained of musculoskeletal pain in the context of secondary hyperparathyroidism, which improved with parathyroidectomy aged 26 years. At age 41 years, he had an abdominal/pelvic CT scan which revealed atrophic, calcified, native kidneys contain-

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Table 1. Serum biochemistry and urinalysis of siblings

	Sibling 1		Sibling 2	
Age, years:	9	23	1	17
Serum biochemistry				
Sodium (mmol/L)	138	138	137	140
Potassium (mmol/L)	3.7	3.9	3.6	2.9
Urea (mmol/L)	8.9 (2.5–6.5)	44.1	5.9 (2.5–6.5)	9.2
Creatinine (μmol/L)	90 (35–75)	1246	51 (10–65)	179
Adjusted calcium (mmol/L)	N/A	2.62	2.46	N/A
Inorganic phosphate (mmol/L)	N/A	3.33 (0.8–1.5)	1.10 (0.9–1.8)	N/A
Alkaline phosphatase (IU/L)	468 (135–557)	204 (30–130)	335 (130–340)	222 (30–130)
Urinalysis				
Microscopic haematuria	No	+	Non-persistent	+
Proteinuria	No	+3	No	>3g/L
Other			'crystals'	

ing multiple cysts and an asymptomatic 2 mm calculus within a mid-pole calyx.

CASE REPORT SIBLING 2

The younger brother of sibling 1 volunteered as a kidney donor for transplantation, aged 17 years. Past medical history was of nocturnal enuresis and polydipsia at 3 years, febrile seizures, generalized developmental delay (walking and talking), short stature, obesity and cryptorchidism. He had an elevated serum creatinine (179 mmol/L) consistent with CKD (see Table 1). He was hypokalaemic (serum potassium 2.9 mEq/L). He also had microscopic haematuria and proteinuria (>3 g/L). A kidney biopsy revealed 2/10 glomeruli with global sclerosis. There was patchy tubular atrophy and patchy interstitial fibrosis with occasional thickening of the tubular basement membrane. Numerous hyaline casts were seen within the tubular lumen. Immunofluorescence was negative, and there was no evidence of nephrocalcinosis. His CKD progressed, and he received a kidney transplant. A plain radiograph of the kidney, ureter and bladder reported no visible calculi and demonstrated diffusely osteosclerotic bones thought related to hyperparathyroidism. He underwent a parathyroidectomy aged 24 years.

The two brothers had whole genome sequencing via the UK 100 000 Genomes Project due to unexplained kidney failure in young people. The project was a hybrid research-clinical project that completed recruitment in December 2018. Both brothers had a hemizygous protein-truncating loss of function variant in *CLCN5* on chromosome Xp11.22 (c.1249C>T; p.Arg417Ter) reported back by the clinical pipeline of the project (see Supplementary data). This was confirmed by Sanger sequencing at the Wessex Regional Genetics Laboratory. This variant is absent in the genome aggregation database (gnomAD) and has not been previously reported in the literature. The variant was classified as pathogenic according to the American College of Medical Genetics guidelines.

DISCUSSION

The hallmark of Dent disease is LMW proteinuria (present in 99%–100% of cases) resulting from proximal tubular dysfunction and occurring early in the disease course [2, 3]. However, only a minority of patients (~10%) are reported to have complete Fanconi syndrome with phosphaturia, aminoaciduria and glycosuria along with osteomalacia or rickets [3]. LMW proteinuria was not tested in this family as there was no clinical suspicion of Fanconi syndrome. Hypercalciuria is also common in Dent disease (~92%–100%) [3]. Conversely, nephrocalcinosis (42%) and nephrolithiasis (32%) are less common with significant inter- and intra-familial variability [1, 3]. This family had no history of nephrolithiasis or nephrocalcinosis, and there was no evidence of hypophosphatemia. Therefore, an analysis of urine calcium was not performed.

The brothers reached ESKD by age 21 and 23 years without clinically evident nephrocalcinosis. This is consistent with a cohort of 108 patients, which showed no statistically significant difference in the rate of CKD progression and the presence of nephrocalcinosis [3]. Kidney biopsy of sibling two, although non-specific with some glomerulosclerosis and chronic tubulointerstitial fibrosis and atrophy, revealed multiple hyaline casts consistent with previous reports in Dent disease type 1 [4].

A similar nonsense variant (c.1039C>T p.Arg347Ter) is previously reported with mild phenotypes, including a 7-year-old from Japan with LMW proteinuria and normal kidney function [2]. A 4-year-old from Turkey had the same p.Arg347Ter mutation with a similar phenotype in addition to a Bartter-like syndrome of hypokalaemic metabolic alkalosis and secondary hyperreninaemic hyperaldosteronism not previously described in Dent disease [5]. These latter features may be consistent with sibling two, who had hypokalaemia requiring supplementation.

These cases suggest that Dent disease should be considered not only in patients with the complete phenotype but also in those with partial or atypical phenotypes, including isolated unexplained CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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have also funded research infrastructure. The 100 000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support. The National Genomics Research and Healthcare Knowledgebase v5, Genomics England. doi:10.6084/m9.figshare.4530893.v5. 2019.

ETHICAL APPROVAL

The 100 000 Genomes Project has approval from the HRA Committee East of England—Cambridge South (REC Ref 14/EE/1112).

PATIENT CONSENT

Written consent to publish this case report was received from the patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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