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Dent disease manifesting as nephrotic syndrome

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SUMMARY Dent disease is an X-linked recessive renal tubular disorder, which is mainly caused by mutations of the *CLCN5* gene and *OCRL* gene. It is characterized by low molecular weight proteinuria, hypercalciuria, nephrocalcinosis or nephrolithiasis, and progressive renal failure. Nephrotic syndrome is a glomerular disorder characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. In this study, we report two cases of Dent disease manifesting as nephrotic syndrome. Two patients were initially diagnosed with nephrotic syndrome due to edema, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia, and responded to prednisone and tacrolimus therapy. Genetic testing revealed mutations in the *OCRL* and *CLCN5* genes. They were eventually diagnosed with Dent disease. Nephrotic syndrome is a rare and insidious phenotype of Dent disease, and its pathogenesis is not fully understood. Patients with nephrotic syndrome are recommended to routinely undergo urinary protein classification and urinary calcium testing, especially those with frequently recurrent nephrotic syndrome and poor response to steroid and immunosuppressive therapy. To date, there is no effective drug treatment for Dent disease. About 30% to 80% of patients progress to end-stage renal disease at the age of 30-50.

Keywords Dent disease, nephrotic syndrome, low molecular weight proteinuria, *CLCN5* gene, *OCRL* gene

1. Introduction

Dent disease (MIM 300009) is a rare genetic renal tubular disorder, with X-linked recessive inheritance. It is generally believed that the main clinical manifestations of Dent disease are low molecular weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis, nephrolithiasis, and progressive renal failure (*1*). The *CLCN5* gene and *OCRL* gene are responsible for Dent disease 1 and Dent disease 2, respectively. About 25% of patients with the phenotype of Dent disease that the two genes cannot explain are classified as Dent disease 3 (*2*). The *CLCN5* gene is located at chromosome Xp11.23 and encodes 2-chloride (Cl-)/proton (H+) exchanger ClC-5, which is expressed in several tissues including brain, liver, renal and intestinal epithelia (*3*). In the kidney, as is known to all, ClC-5 is highly expressed in the distal nephron and proximal tubules (*4*). ClC-5 is indispensable for reabsorbing low molecular weight proteins through receptor- and non-receptor-mediated endocytosis in the proximal tubule (*5*). Additionally, studies have shown that ClC-5 is overexpressed in the glomeruli of proteinuric patients, and may have a role in protein endocytosis (*6*). The *OCRL* gene is located at chromosome Xq26.1 and encodes a phosphatidylinositol 4,5-bisphosphate-5-phosphatase (PIP2), widely expressed in the glomerulus and almost all of the tubular segments (*7*). Nephrotic syndrome (NS) is a glomerular disorder characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. It includes congenital nephrotic syndrome, primary nephrotic syndrome, and secondary nephrotic syndrome (*8*). NS is a rare and unstable phenotype of Dent disease, and its pathogenesis is still unclear (*9*).

Here, we present two cases of Dent disease presenting as NS. This study is consistent with the Declaration of Helsinki. Written consent was obtained from the patient's family. The Ethics Committee of the Second Xiangya Hospital of Central South University exempted the ethical approval of this study.

2. Clinical data

Patient 1 was diagnosed with NS for edema, proteinuria, hypoalbuminemia, and hyperlipidemia at the age of 4 years. After prednisone treatment, edema and proteinuria still frequently recurred. In 2021, at the age of 11, he received treatment at The Xiangya Second Hospital of Central South University. His weight was 24 kg and height was 125 cm. He was normotensive on admission (99/54 mmHg), with mild peripheral edema. The

laboratory findings were as follows: white blood cell count 7.41 × 10^9/L, hemoglobin 114 g/L, and platelets 402 × 10^9/L. Serum albumin 14.3 g/L, total protein 37 g/L. His urinalysis revealed 3+protein, and the quantity of 24h urinary protein was 3850.65 mg (160.44 mg/kg). Immunology tests showed low levels of IgG and high levels of IgE. IgA and IgM were within the normal range. C3 and C4 levels were within the normal range. Also, antinuclear antibodies, anti-ENA antibodies, and anti-dsDNA antibodies were all negative.

Renal ultrasound showed that both kidneys were of normal size, with no evidence of nephrocalcinosis or nephrolithiasis. Light microscopy revealed the glomeruli were swollen, mesangial cells and mesangial matrix proliferated, and the glomerular basement membrane was normal. Partial renal tubular epithelial cell vacuolar degeneration, renal interstitial focal edema, fibrosis, and inflammatory cell infiltration was observed. Obvious inflammatory changes could be seen in renal arterioles. Immunofluorescence revealed IgM++. Electron microscopy revealed extensive glomerular fusion of foot process and segmental sclerosis, considering focal segmental glomerulosclerosis (FSGS). The boy was tentatively diagnosed with IgM nephropathy. Genetic testing indicated a novel duplication of exons 7 to 8 of the *OCRL* gene. His mother was identified as a carrier for the same *OCRL* gene mutation. The patient was eventually diagnosed with Dent disease 2.

Patient 2 was diagnosed with NS for edema, proteinuria, hypoalbuminemia, and hyperlipidemia at the age of 5 years. His urine protein returned to normal and edema was relieved after receiving prednisone treatment. However, during the process of gradual reduction of prednisone, edema and proteinuria recurred frequently. In 2018, at the age of 8, the boy was referred to The Second Xiangya Hospital of Central South University. His weight was 49 kg and height was 125 cm. He was normotensive on admission (96/65 mmHg). The laboratory findings were as follows: white blood cell count 13.08 × 10^9/L, hemoglobin 131 g/L, platelets 360 × 10^9/L, serum albumin 10.5 g/L, and total protein 31.4 g/L. His urinalysis revealed 3+protein, the quantity of 24h urinary protein was 13,703.24 mg (279.66 mg/kg). Immunology tests showed low levels of IgG and IgA. IgM and IgE were within the normal range. C3 levels were below normal range, C4 levels were within the normal range. Also, antinuclear antibodies, anti-ENA antibodies, and anti-dsDNA antibodies were all negative.

Renal ultrasound showed that both kidneys were of normal size, with no evidence of nephrocalcinosis or nephrolithiasis. He did not undergo a kidney biopsy. The boy was tentatively diagnosed with NS. Genetic testing indicated a hemizygous mutation of the *CLCN5* gene c.796A>G (p.I266V), confirming the diagnosis of Dent disease 1. His mother was identified as a carrier for the same *CLCN5* gene mutation.

The clinical manifestation and laboratory tests are summarized in Table 1.

Table 1. Clinical manifestation and laboratory tests of our patients

Items	Patient 1	Patient 2
Gender	male	male
Age of onset (years)	4	3
Current age (years)	11	12
Blood pressure (mmHg)	99/54	96/65
Chief complaint	edema and proteinuria	edema and proteinuria
Urine investigations		
Urine protein	3+	3+
24 h protein (mg/kg)	160.44	279.66
Microalbumin (mg/L)	10	-
Alpha1-microglobulin (mg/L)	-	-
Beta 2-microglobulin (mg/L)	-	-
Retinol-binding protein (mg/L)	-	-
Urine calcium/ urine creatinine (mg/mg)	-	-
24 h urine calcium (mg/kg)	-	-
Nephrocalcinosis/nephrolithiasis	No	No
Kidney biopsies		
Light microscopy	IgM nephropathy	-
Electron microscopy	FSGS	-
Blood investigations		
Serum albumin (g/L)	14.3	10.5
Serum sodium (mmol/L)	138.0	127.9
Serum potassium (mmol/L)	3.26	3.11
Serum chlorine (mmol/L)	105.8	94.8
Serum calcium (mmol/L)	1.51	1.69
Serum phosphate (mmol/L)	1.24	0.97
Serum creatinine (μmol/L)	31	28.1
eGFR (mL/min/1.73 m^2)	195.97	216.19
Uric acid (μmol/L)	439.0	727.6
Urea (mmol/L)	4.90	6.32
IgG (g/L)	2.11	0.62
IgA (g/L)	1.08	2.13
IgM (g/L)	1.88	1.96
IgE (ng/mL)	1694.00	440.20
Serum C3 (g/L)	1.28	0.62
Serum C4 (g/L)	0.34	0.19

3. Discussion

In this study, we present two cases of Dent disease manifesting as NS. Two patients all clinically featured recurrent edema, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia, and were initially diagnosed with NS. Genetic testing revealed mutations of the *OCRL* gene and *CLCN5* gene, confirming the diagnosis of Dent disease 2 and Dent disease 1, respectively. The genetic testing results of our patients are showed in Table 2. To our knowledge, the mutations of the *OCRL* gene (duplication of exons 7 to 8) and *CLCN5* gene c.796A>G (p.I266V) have not been reported so far (*1,2*).

Gianesello L, *et al.* conducted a literature review and found that 55 Dent disease 1 patients and 20 Dent disease 2 had nephrotic range proteinuria (37% and 48% respectively of the collected literature). These patients were found to have varying degrees of glomerular dysfunction, though Dent disease is widely accepted as

Table 2. Genetic testing results of our patients

Items	Patient 1	Patient 2
Gene mutation	*OCRL1*	*CLCN5*
Nucleotide change	exon 7-8 repeats	c.796A>G
Amino acid change	-	p.I266V
Type of mutation	-	missense mutation
Mutation source	mother	mother

a proximal tubulopathy disorder (*2*). Guohua He *et al.* reported that the urinary α1-microglobulin/albumin ratio was considered to be a useful parameter to differentiate LMWP caused by Dent disease from albuminuria caused mainly by NS (*10*). Makino S, *et al*. reported that the urine β2-MG/urine protein can be used to monitor the relapse of NS in patients with Dent disease, as it is consistent with the progression of NS (*10*).

Dent disease is an inherited renal tubular disorder. It is characterized by LMWP, hypercalciuria, nephrocalcinosis, nephrolithiasis, and progressive renal failure. A large Dent disease study analyzed data from 109 male patients with *CLCN5* mutations and 9 patients with mutations of the *OCRL1* gene. They observed that the phenotype of Dent disease 1 and Dent disease 2 was similar, and with age, the phenotype evolves from mainly proximal nephropathy to a mixed proximal/distal salt-losing tubulopathy (*11*). Proteinuria apparently worsened with age, while hypercalciuria gradually resolved as renal function worsened. Also, estimated GFR has been shown to correlate with the degree of interstitial fibrosis.

The urine protein of patients with Dent disease is mostly mild to moderate, NS is a rare and insidious phenotype of Dent disease. The traditional view is that if NS patients do not respond to hormones and immunosuppressant therapy, the possibility of hereditary kidney disease should be considered. While in this research, two patients were initially diagnosed with NS and responded to prednisone and tacrolimus therapy. This means that the classification of urine protein and the detection of urinary calcium needs to be carried out routinely. LMWP is a characteristic clinical phenotype of Dent disease, and there is no significant difference between Dent disease 1 and Dent disease 2 (*9*). Long-term proteinuria may be an important factor in renal function injury in patients. Are patients with Dent disease manifesting as NS more likely to develop renal insufficiency? The specific pathogenesis of Dent disease manifesting as NS needs further study.

The relationship between genotype and phenotype of Dent disease remains unestablished. Patients with the same gene mutation site can induce different clinical phenotypes, even in the same family. In 2008, two brothers were reported with identical variants of the *CLCN5* gene (c.473G>A, p.Gly158Asp) in Denmark. The patient had nephrocalcinosis, proteinuria, hypercalciuria, and was diagnosed with Dent disease, whereas the patient's brother was asymptomatic with laboratory findings all within the normal range (*12*). In 2017, two Chinese brothers were reported to both carry the hemizygous mutation c.731C>T (p.S244L) in exon 7 of the *CLCN5* gene, but they had different phenotypes (*13*). The elder brother presented with nephrotic range LMWP, aminoaciduria, polydipsia, polyuria, nephrocalcinosis, hypophosphatemia, hypokalemia, acidosis, hyposthenuria, and rickets but without hypercalciuria. He was finally diagnosed with Fanconi syndrome. However, the younger brother presented with nephrotic-range LMWP, hypercalciuria, and aminoaciduria, and was diagnosed with Dent disease.

To date, there is no effective treatment for Dent disease. The main therapeutic goals are to reduce hypercalciuria, prevent renal calcification, and delay the progression of renal failure (*1*). A high amount of drinking water, a low calcium diet, and thiazide drugs are still the most effective supportive treatments for Dent disease. Patients diagnosed with Dent disease should be treated with low-dose thiazines and citrate as soon as possible. Approximately 30% to 80% of patients with Dent disease progress to end-stage renal disease at the age of 30–50 (*14*). It is rare for Dent disease to develop into chronic kidney disease in childhood and only a few cases have been reported so far (*15-18*).

4. Conclusion

NS is a relatively rare phenotype of Dent disease. The phenotypic heterogeneity of Dent disease prevents its prompt diagnosis. Both our patients were initially diagnosed with NS and responded to prednisone and tacrolimus therapy. This reminds us that in patients presented as having NS, who respond to steroid and immunosuppressive therapy, the possibility of Dent disease also needs to be considered. Therefore, for patients with proteinuria, urine protein classification and urinary calcium detection should be routinely performed, which is a more economical and convenient method than genetic testing. The pathogenesis of Dent disease manifesting as NS and the mechanism of response to hormones and immunosuppressant therapy needs to be further studied.

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