

## Dent's disease complicated by nephrotic syndrome: A case report

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### Summary

Dent's disease is an X-linked recessive proximal tubular disorder that mostly affects male patients in childhood or early adult life. The condition is caused by mutations in the *CLCN5* (Dent disease 1) or *OCRL* (Dent disease 2) genes located on chromosome Xp11.22 and Xq25, respectively. In most male patients, proteinuria is subnephrotic but may reach nephrotic levels. Here, we report the first case of Dent's disease complicated by nephrotic syndrome. Dent's disease should be considered in the differential diagnosis of nephrotic syndrome, and especially in male patients with early onset of nephrotic syndrome. A urinary  $\alpha$ 1-microglobulin/albumin ratio > 1 may provide the first clue to a tubulopathy.

**Keywords:** Dent's disease, proteinuria, nephrotic syndrome, *OCRL* gene

### 1. Introduction

Dent's disease is an X-linked recessive proximal tubulopathy that presents with hypercalciuria, low-molecular-weight proteinuria (LMWP), nephrolithiasis, nephrocalcinosis, and progressive renal failure (1,2). Dent's disease is divided into two types depending on the phenotype: Dent's disease 1 (OMIM #300009), which is caused by mutations in the *CLCN5* gene located on chromosome Xp 11.22, and Dent's disease 2 (OMIM#300555), which is caused by mutations in the *OCRL* gene located on chromosome Xq25 (3). Dent's disease mainly affects males, whereas female carriers may display a milder phenotype (4,5). Patients are usually diagnosed in childhood or in their early adult years. LMWP is the most consistent feature, occurring in 99% of affected male patients. Proteinuria is usually subnephrotic but may reach nephrotic levels (2,6,7). To the extent known, there are no previous reports on Dent's disease complicated by nephrotic syndrome.

Reported here is a case involving a 4-year-old boy. Consistent with the diagnosis of nephrotic syndrome,

renal pathology indicated minimal change disease (MCD), and mutation analysis indicated a c.2435T>C (p.L812P) mutation in the *OCRL* gene. The boy was found to have Dent's disease complicated by nephrotic syndrome.

### 2. Case Report

A 4-year-old Chinese boy who had intermittent proteinuria (urine protein of 1.91 g/24 h, 172 mg/Kg) and edema for 13 months presented with hypoalbuminemia of 15.3 g/L and hypercholesterolemia of 7.80 mmol/L. The boy was initially treated for nephrotic syndrome at a local hospital; the boy received a full dose of corticosteroids for 8 weeks, 3 doses of intravenous methylprednisolone (MP), and then 8 doses (one dose per month) of cyclophosphamide (CTX). The boy then received oral prednisone and mycophenolate mofetil (MMF) for 4 months. The boy's proteinuria appeared to subside but did not completely resolve (urine protein of 0.45-1.11 g/24 h). The boy was referred to this Hospital on August 1, 2015. An examination at admission indicated a height of 90 cm and weight of 11 Kg, both of which were below the 1<sup>st</sup> percentile. A 24-h urine collection at this Hospital revealed urine protein of 0.48 g/24 h (44 mg/Kg). Urinalysis revealed urine  $\alpha$ 1-microglobulin of 307 mg/L and urine albumin of 103 mg/L. The boy's urine  $\alpha$ 1-microglobulin/albumin ratio was > 1. Urine protein electrophoresis was performed, and the pattern revealed a low-molecular-weight protein fraction

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**Table 1. Clinical data from different times the current patient was hospitalized**

Hospitalization	Status of NS	Alb (g/L)	Cholesterol (mmol/L)	UPE (mg/kg/24h)	$\alpha$ 1 MG (mg/L)	MicroAlb (mg/L)	$\alpha$ 1 MG/albumin	Low-molecular-weight protein fraction (%)	Treatment
1 <sup>st</sup>	remission	40.0	5.06	0.48	307	103	2.98	64.4	Pre + MMF
2 <sup>nd</sup>	relapse	17.3	16.13	4.33	208	3,106	0.07	10.1	Pre
3 <sup>rd</sup>	remission	30.5	8.79	0.90	208	138	1.51	61.7	Pre
4 <sup>th</sup>	relapse	27.5	10.96	2.01	462	1,452	0.32	29.8	Pre
5 <sup>th</sup>	remission	38.1	6.13	0.68	366	234	1.56	63.1	Pre + CsA

Alb: albumin; CsA: cyclosporine; MG: microglobulin; MMF: mycophenolate mofetil; Pre: prednisone; UPE: urinary protein excretion;  $\alpha$ 1MG:  $\alpha$ 1-microglobulinuria.

of 64.4%. Hypercalciuria (0.18 mmol/Kg/24h, ratio of urine calcium to creatine = 0.32) was also noted. Further investigation revealed normal creatine (49.2  $\mu$ mol/L) and an estimated glomerular filtration rate (eGFR) of 100 mL/min/1.73 m<sup>2</sup>. A chemistry panel revealed a serum albumin level of 44 mg/L and a cholesterol level of 5.06 mmol/L. The boy's autoimmune profile, including C3 and C4 complements, was normal. Serum phosphate was 1.66 mmol/L (1.45-2.1 mmol/L), alkaline phosphatase was 147 U/L (< 750 U/L), and serum calcium was 2.42 mmol/L (2.11-2.52 mmol/L).

Renal ultrasonography revealed no evidence of abnormalities. Renal biopsy indicated normal glomeruli with minimal proliferation of mesenteric cells and matrix, vacuolar degeneration of the glomerular basement membrane, and vacuolar and granular degeneration of tubular epithelium. Immunofluorescence was negative. Electron microscopy (EM) revealed segmental fusion of epithelial foot processes but no obvious abnormalities in tubules. The results of EM coincided with glomeruli minimal change. The boy was tentatively diagnosed with minimal-change disease (MCD). A genetic test indicated a heterozygote mutation of the *OCRL* gene c.2435T>C (p.L812P), confirming the diagnosis of Dent's disease 2. The boy's mother was subsequently identified as a carrier for the same *OCRL* gene mutation. The child's Gesell adaptive score was normal except for a slight delay in language development. An ophthalmological examination revealed congenital cataracts (zonular).

Hydrochlorothiazide (1 mg/Kg daily) was given orally as primary treatment as soon as the diagnosis of Dent's disease 2 was confirmed. Potassium citrate was also given orally, and immunosuppressive agents were gradually tapered off. Over a follow-up of 9 months, the patient had no recurrence of edema, urine protein of 0.42-0.51 g/24h, and urine calcium of 0.89-1.35 mmol/24 h (0.08-0.12 mmol/Kg/24h); all of the parameters had improved markedly.

Nine months after diagnosis (08/10, 2015), the boy had recurrence of edema, oliguria, and an increase in urine protein from 1+ to 3+ after an upper respiratory infection. A 24-h urine collection revealed urine protein of 4.33 g/24h. A chemistry panel revealed serum albumin of 17.3 g/L and cholesterol of 16.13 mmol/L. The boy's urine  $\alpha$ 1-microglobulin/albumin ratio was < 1 (urine  $\alpha$ 1-microglobulin of 208 mg/L and urine albumin of 3,106

mg/L). The pattern of urine protein electrophoresis revealed a low-molecular-weight protein fraction of 9.1%, an albumin fraction of 69.0%, and a high-molecular-weight protein fraction of 21.9%. The boy's urine calcium/creatinine ratio and 24-h urine calcium were normal. At this stage, relapse of nephrotic syndrome was considered, so the boy was started on 60 mg/m<sup>2</sup> of prednisone. Two weeks later, urine protein decreased to 1.83 g/24h and serum albumin increased to 30 g/L. After four weeks of a full dose of prednisone, the drug was gradually tapered off. A chemistry panel revealed serum albumin of 30.5-44.2 g/L. A 24-h urine collection revealed urine protein of 0.9-1.1 g/24h, urine calcium of 1.53-1.85 mmol/24h. Urinalysis revealed urine  $\alpha$ 1-microglobulin of 208-321 mg/L and urine albumin of 183-219 mg/L.

Three months after the first relapse (21/01, 2016), the boy was admitted for reevaluation while taking 25 mg of prednisone (1.78 mg/Kg) every other day. The boy had no obvious edema. A 24-h collection of urine revealed urine protein of 2.01 g/24h. A chemistry panel revealed serum albumin of 27.5 g/L and cholesterol of 10.96 mmol/L. The boy's urine  $\alpha$ 1-microglobulin/albumin ratio was < 1 (urine  $\alpha$ 1-microglobulin of 462 mg/L and urine albumin of 1452 mg/L). The pattern of urine protein electrophoresis revealed a low-molecular-weight protein fraction of 29.8%, an albumin fraction of 64.6%, and a high-molecular-weight protein fraction of 5.6%. A 2<sup>nd</sup> relapse of nephrotic syndrome was considered although there was no obvious edema. The dose of oral prednisone was increased to 1 mg/Kg daily and cyclosporine was added at a total daily dose of 3.3 mg/Kg (a half dose 2 times per day). Two weeks after the adjustment, urine protein decreased to 0.98 g/24h. The dose of prednisone was gradually reduced, and the boy's course was satisfactory at a 6-month follow-up; his urine protein maintained stable and renal function was within the normal range (Table 1).

### 3. Discussion

Dent's disease is an X-linked recessive proximal tubular disorder that mostly affects male patients in childhood or early adult life. In most male patients, proteinuria is subnephrotic but may reach nephrotic levels (8,9). The current report describes the first case of Dent's disease

complicated by nephrotic syndrome.

A 4-year-old boy presenting with intermittent edema, persistent proteinuria at a nephrotic level, transient hypoalbuminemia, and hyperlipidemia responded somewhat to glucocorticoids (GC) and other immunosuppressive agents. However, his urine protein did not return to normal. Further investigation revealed hypercalciuria, hypercholesterolemia, retardation of growth, and congenital cataracts. Renal biopsy led to a tentative diagnosis of MCD, and genetic testing revealed a c.2435T>C (p.L812P) mutation in the *OCRL* gene. Dent's disease was diagnosed based on the presence of LMWP, hypercalciuria, retardation of growth, and congenital cataracts, and this diagnosis was confirmed based on a mutation in the *OCRL* gene (3). Nephrotic syndrome was diagnosed based on the presence of edema, severe proteinuria (172 mg/Kg), hypoalbuminemia (15.3 g/L), and hypercholesterolemia of 7.8 mmol/L, and this diagnosis was confirmed based on pathologic evidence of MCD under light microscopy and fusion of epithelial cell foot processes on EM. Thus, the current patient had Dent's disease complicated by nephrotic syndrome.

Dent's disease and nephrotic syndrome are two distinct diseases. A look at the pathogenesis of proteinuria in these two diseases indicates that proteinuria originates due to two different processes. In idiopathic nephrotic syndrome (INS), proteinuria is mainly albuminemia, so hypoalbuminemia is commonly found in INS with substantial albumin loss *via* urine. Non-specific histological abnormalities of the kidney, including minimal changes, focal and segmental glomerular sclerosis (FSGS), and diffuse mesangial proliferation, are present in INS. Glomeruli had a fusion of epithelial cell foot processes on EM and no significant deposits of immunoglobulins or complements according to immunofluorescence. In Dent's disease, however, proteinuria is mainly LMWP. LMWP is a result of tubular dysfunction that prevents effective reabsorption of low-molecular-weight proteins, including  $\alpha$ 1 and  $\beta$ 2 microglobulins, retinol-binding protein (RBP), Clara cell protein, and vitamin D binding protein, that are filtered through the glomerular basement membrane (10-12). However, albuminuria will be produced when there are defects in the glomerular basement membrane. In some cases, Dent's disease manifests as proteinuria in the nephrotic range, which is a combination of albuminuria and LMWP. This indicates that both of the aforementioned processes can occur in the same patient. That said, none of the reported patients had hypoalbuminemia, indicating that LMWP is the primary cause of proteinuria while albuminuria is only slight cause of proteinuria in Dent's disease. In other words, Dent's disease and nephrotic syndrome were two independent diseases in the current case.

The current treatment for Dent's disease is mainly supportive, including hydrochlorothiazide (HCTZ) and

potassium citrate in order to prevent nephrolithiasis (13-15). In contrast, the treatment for nephrotic syndrome is mainly immunosuppressive agents, with glucocorticoids (GC) being the agent of choice. In cases of Dent's disease complicated by nephrotic syndrome, both of those treatments should be used. The dose of GC should be reduced as the disease subsides, while HCTZ and potassium citrate should be maintained. The question then is how to evaluate the efficacy of treatment. How can the dose of GC be reduced while urine protein remains positive?

$\alpha$ 1-Microglobulin has long been considered an effective biomarker of tubular dysfunction (16,17). A study found a correlation between  $\alpha$ 1-microglobulin and albuminuria in diabetic children (17), which could indicate tubular dysfunction is present in diabetes. In Dent's disease, urinary  $\alpha$ 1-microglobulin increases significantly due to the pathological changes occurring mainly in tubules. In the current case, the ratio of urine  $\alpha$ 1-microglobulin to albumin proved to be a useful indicator of LMWP. The patient's 24-h urine protein level was monitored and the patient's urine  $\alpha$ 1-microglobulin/albumin ratio was calculated. When nephrotic syndrome was adequately controlled, the patient's 24-h urine protein level tended to be lower, but LMWP caused by Dent's disease resulted in urine protein remaining positive. The patient's urine  $\alpha$ 1-microglobulin/albumin ratio was monitored when nephrotic syndrome relapsed. The patient had severe albuminuria and an  $\alpha$ 1-microglobulin/albumin ratio far below 1. Urine protein was monitored when the recurrence of nephrotic syndrome was under control. The patient's urine protein decreased back to its usual level and the patient's urine  $\alpha$ 1-microglobulin/albumin ratio increased from far below 1 to more than 1. At this point, nephrotic syndrome was apparently under control even though urine protein was still positive (Table 1). The protein in urine was presumably due mainly to the LMWP caused by Dent's disease. When nephrotic syndrome was consistently controlled, the  $\alpha$ 1-microglobulin/albumin ratio remained more than 1.

In conclusion, reported here is the first case of Dent's disease complicated by nephrotic syndrome, which is significant since Dent's disease and nephrotic syndrome are two independent diseases. A urine  $\alpha$ 1-microglobulin/albumin ratio > 1 was successfully used as a parameter to differentiate LMWP caused by Dent's disease from albuminuria caused mainly by relapsing nephrotic syndrome, suggesting that this parameter could be used as a diagnostic marker of tubular proteinuria.

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