

CASE REPORTS

Dent disease: A cause of proteinuria against all odds

Doença de Dent: Uma causa improvável de proteinúria

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ABSTRACT

Dent disease is a rare X-linked progressive renal disease characterized by hypercalciuria and low molecular weight proteinuria. In early childhood, patients may manifest only proteinuria and/or hypercalciuria, both of which are generally asymptomatic.

The authors report three cases of male patients with asymptomatic, non-orthostatic nephrotic proteinuria first detected during screening for an acute condition. All had intermittent hypercalciuria, one had nephrocalcinosis, and one had mild hypotonia and some learning difficulties. Genetic testing identified pathogenic variants in all patients, two in the OCRL gene and one in the CLCN5 gene. To date, none have developed chronic kidney disease.

The diagnosis of Dent disease can be challenging, but it should be considered in all men with unexplained proteinuria. This approach may not only allow for earlier diagnosis, but also avoid unnecessary testing and potentially harmful treatments.

Keywords: CLCN5; Dent disease; hypercalciuria; OCRL; proteinuria

RESUMO

A doença de Dent é uma tubulopatia rara e progressiva ligada ao cromossoma X, caracterizada por hipercaleiúria e proteinúria de baixo peso molecular. Na primeira década, os doentes manifestam apenas proteinúria e/ou hipercaleiúria, sendo ambas geralmente assintomáticas. Posteriormente, os sintomas podem evoluir para insuficiência renal crónica.

São apresentados três casos de crianças do sexo masculino com proteinúria nefrótica não ortostática assintomática detetada em contexto de doença aguda. Todas as crianças apresentaram hipercaleiúria intermitente, uma apresentou nefrocalcinose e outra hipotonia ligeira e dificuldades de aprendizagem. O estudo genético identificou variantes patogénicas em todos os doentes, duas no gene OCRL e uma no gene CLCN5. Nenhum doente apresentou deterioração da função renal.

O diagnóstico de doença de Dent pode ser desafiante, devendo ser considerado em casos de proteinúria inexplicável no género masculino. Esta abordagem permitirá, não só antecipar o diagnóstico, como evitar investigação e tratamentos desnecessários.

Palavras-chave: CLCN5; doença de Dent; hipercaleiúria; OCRL; proteinúria

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INTRODUCTION

Dent disease (DD) is a rare X-linked renal proximal tubular disorder characterized by low molecular weight (LMW) proteinuria and hypercalciuria. Nephrocalcinosis and nephrolithiasis may also be present, leading over time to chronic kidney disease (CKD).⁽¹⁻⁸⁾

DD comprises two genetic subtypes: up to 60% of patients have inactivating pathogenic variants of the CLCN5 gene at chromosome Xp11.23 (Dent-1), and about 15% have pathogenic OCRL variants at chromosome Xq26.1 encoding a phosphatidylinositol 4,5-bisphosphate 5-phosphatase (Dent-2).^(1,2,4) No specific gene defect has been described in the remaining 25%.^(2,4)

The renal phenotype of Dent-2 is comparable to that of Dent-1, except for a lower prevalence of nephrocalcinosis.^(1,3,5) Since CLCN5 and OCRL1 mutations impair the megalin-cubilin system (MCS), loss of

LMW proteins is a universal finding in DD, and persistent proteinuria is a known renal injury.^(1,4,5) Hypercalciuria is present in up to 90% of patients with confirmed DD.⁽⁵⁾ Other signs of proximal tubule dysfunction, namely glycosuria, aminoaciduria, and phosphaturia, are also common features, and mild hypophosphatemia occurs in approximately one third of patients.^(1,4,5)

The disease has a marked male predominance, with symptomatic disease mainly confined to males.⁽¹⁻⁶⁾ In the first decade of life, children may manifest only LMW proteinuria and/or hypercalciuria, both of which are usually asymptomatic, making the diagnosis quite challenging.^(1,3,4)

Herein are reported three cases of DD referred to a Pediatric Nephrology Department for asymptomatic proteinuria first detected during screening for an acute condition (complementary data on **Table 1**).

Table 1 - Clinical and anthropometric data of male patients with Dent disease at the time of initial evaluation and complementary examination. For laboratory parameters, the results shown correspond to the time of diagnosis.

Items	Case 1	Case 2	Case 3		
Age at presentation (Y)	1	9	10		
Atual age (Y)	9	18	13		
Weight (kg)	10.4 (-0,35 SD)	21.6 (-2,7 SD)	39.4 (+0,31 SD)		
Length / height (cm)	75.6 (-1,45 SD)	123.5 (-2.2 SD)	140.8 (-0,71 SD)		
Blood pressure (mmHg)	85/49 (<P90)	85/54 (<P90)	97/60 (<P90)		
Physical examination	Macrocephaly (+2.01 SD)	Mild eyelid edema	Normal		
Psicomotor Development	Hypotony, learning difficulties	Normal	Normal		
Urine collection's context	Fever	Recurrent abdominal pain	Abdominal pain	Reference Range	
Serum investigation	BUN (mg/dL)	6.8	6.7	7.1	5 - 18
	Creatinine (mg/dL)	0.37	0.57	0.64	0.57 - 0.88
	Albumin (g/L)	46	45	42	37 - 56
	Total Protein (g/L)	86.5	74	68	57 - 80
	Inorganic Phosphate (mg/dL)	5.9	5.2	4.9	4.5 - 5.5
	Uric Acid (mg/dL)	3.68	4.71	2.91	2.35 - 5.88
	Parathormone (pg/mL)	12	29	32	8 - 51
	25-Hidroxovitamin D (ng/mL)	30	Not performed	14	>20
Urine investigation	Protein	2+	2+	3+	negative
	B2-Microglobulin (mg/L)	114	50	31	<2.5
	UTP (mg/m ² /h)	1053	103	48	<4
	Calcium (mg/kg/24h)	4	7	4.1	<4
	PRR (%)	79	Not performed	91	<2Y: 81-89 ≥2Y: 90-95
	Amino acid chromatography	Not performed	Negative	Negative	
Renal ultrasound	Normal	Normal	Medullary nephrocalcinosis		
Kidney biopsy	Not performed	Normal	Not performed		
Genetic study	OCRL	OCRL	CLCN5		
Allelic variant	c.1713G>A, p.(Glu571Glu)	c.1568A>T, p.(Asp523Asp)	Not available		

BUN – Blood Urea Nitrogen; P- Percentile; PRR – Phosphorus reabsorption rate; SD – Standard deviation, UTP – Urinary total protein; Y – Years

CLINICAL CASES

Case 1:

A fifteen-month-old male child was diagnosed with proteinuria during an episode of acute febrile tonsillitis. His personal and family history was unremarkable (**table 1**). His daily milk intake was approximately 500 milliliters and he was on vitamin D supplementation. The boy had macrocephaly (50.3 cm; +2.01 standard deviation [SD]) with ventriculomegaly. Mild hypotonia was noted initially, and learning difficulties were noted later in the preschool years. The remaining physical examination was unremarkable. Laboratory studies revealed mixed (tubular and glomerular) nephrotic proteinuria (NP) and intermittent hypercalciuria. DNA sequencing revealed a pathogenic mutation in the maternally inherited OCRL gene.

The last analytical control at the age of nine years (without treatment) showed normal kidney function and a protein/creatinine ratio in occasional urine sample of 1.97 mg/mg.

Case 2:

A nine-year-old boy presented with proteinuria detected on urinalysis requested due to recurrent abdominal pain. He had an acute febrile nasopharyngitis the previous week (**table 1**). The boy played football twice a week, but there was no history of trauma and no apparent temporal relationship of the condition to exercise, and no relevant family or personal history except for low weight and height for age. The parents reported predominantly morning eyelid edema. There were no other significant findings on examination.

Laboratory study revealed non-orthostatic mixed NP and hypercalciuria. Renal ultrasound and blood pressure were normal. At ten years of age, the boy was treated with enalapril, with incremental daily doses up to 0.3 mg/kg because of the increase in urea and creatinine. Three years later, height-weight deceleration was evident and subsequent endocrine evaluation was negative. Kidney biopsy was normal and genetic study revealed a *missense* hemizygous variant in the OCRL gene.

At the time of the last observation, at the age of eighteen years, before the transition to adult care, the boy had no complaints and there were no physical findings. The last analytical evaluation, under enalapril, showed normal kidney function and a protein/creatinine ratio in occasional urine sample of 1.80 mg/mg.

Case 3:

A ten-year-old boy presented with proteinuria during evaluation for abdominal pain associated with *Campylobacter jejuni* gastroenteritis. His personal and family history was unremarkable (**table 1**).

Physical examination revealed no abnormalities except for *pectus excavatum*. Complementary study revealed non-orthostatic mixed NP and intermittent hypercalciuria. Renal ultrasound was compatible with medullary nephrocalcinosis. DNA sequencing revealed a hemizygous pathogenic deletion in the CLCN5 gene.

At 13 years of age, the boy's renal function was normal and he

maintained significant non-nephrotic proteinuria (36 mg/m²/hour) without treatment.

DISCUSSION

DD is a progressive kidney disease characterized by hypercalciuria, LMW proteinuria, and other signs of proximal tubular dysfunction such as hypophosphatemia and acidosis.⁽¹⁻⁸⁾ Clinical diagnosis requires evidence of LMW proteinuria, hypercalciuria, and at least one of the following criteria: nephrocalcinosis, nephrolithiasis, hypophosphatemia, hematuria, or renal insufficiency.⁽¹⁻⁸⁾ However, in children under the age of ten, only LMW proteinuria and/or hypercalciuria may be present, both of which are usually asymptomatic.⁽¹⁻⁸⁾ Molecular testing confirms the diagnosis.

The three reported cases (**table 1**) share several characteristics: they were all males who presented with asymptomatic non-orthostatic NP detected by urinalysis in the setting of screening for an acute condition. According to the literature, half of patients with DD have proteinuria in the nephrotic range, which is often present in early childhood and typically increases with age.^(1,4,5) Therefore, despite the mixed NP due to MCS impairment, these patients usually have normal serum albumin levels and do not develop nephrotic syndrome.^(1,4-6)

Although always detected, hypercalciuria was intermittent, which may have delayed the diagnosis of DD.^(1,8) Moreover, hypercalciuria may even resolve completely with dietary calcium restriction, suggesting intestinal hyperabsorption as the main pathophysiologic mechanism.^(1,3,5,6)

In addition to these renal disease features suggesting selective proximal tubulopathy rather than full Fanconi syndrome, a mutation found in the CLCN5 (case 3) and OCRL (cases 1 and 2) genes confirmed DD.

Furthermore, no alterations in glomerular filtration, lipid profile, autoimmunity, or phosphocalcium metabolism (including hypophosphatemia) have been observed in any of the cases to date. Although approximately 25% of affected males may develop rickets or osteomalacia, most children have normal bone mineral density and attain normal height.^(1,5,6) As illustrated in the second clinical case, patients may have growth restriction and short stature, which is typically mild and subclinical in Dent-1 and more pronounced in Dent-2.^(1,5,6) Children with Dent-2 may also have developmental delay and/or mild intellectual impairment, as illustrated in the first clinical case.^(1,5,6)

Nephrocalcinosis was present in case 2 and it is thought to occur in up to 75% of cases, often in childhood.^(1,6,7)

Kidney biopsy is an invasive diagnostic test with unspecific findings.⁽⁷⁾ It was performed in the second clinical case because of unexplained persistent NP that was not controlled with increasing doses of enalapril, was associated with height-weight deceleration, and predicted significant delay in obtaining molecular test result.

The primary goals of treatment are to reduce hypercalciuria, prevent

nephrocalcinosis, and delay progression to CKD.^(1,2) Angiotensin-converting enzyme inhibitors (ACEI) may reduce proteinuria and delay loss of kidney function, but data on their effectiveness are sparse.^(1,2) ACEI (enalapril) were used only in case 2 in this study due to the persistence of NP on serial analyses.

Approximately two thirds of affected males develop some degree of CKD, with decreased creatinine clearance usually becoming apparent in late childhood.^(1,6) The patient in case 2 had already reached adulthood and no decline in kidney function was observed. For cases 1 and 3, both clinical and analytical follow-up will be mandatory in the coming years.

Overall, the diagnosis of DD is challenging, especially in the absence of a family history, and requires a high degree of clinical suspicion. It should be considered in all male patients with unexplained proteinuria, as it may allow earlier diagnosis and avoid unnecessary kidney biopsies and potentially harmful therapies.^(1,4,8)

AUTHORSHIP

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