RENAL PHENOTYPES OF DENT DISEASE PATIENTS ACCORDING TO THEIR GENOTYPES

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BACKGROUND

Dent disease (DD) is a rare X-linked recessive renal tubulopathy characterized by low-molecular-weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis and/or nephrolithiasis. DD is caused by mutations in both the *CLCN5* gene encoding the electrogenic chloride/proton exchanger ClC-5, which is involved in the tubular reabsorption of albumin and LMW proteins, and in the *OCRL* gene responsible of Lowe syndrome In approximately 25% of patients, no *CLCN5* and *OCRL* mutations have been detected (1).

AIM

The aim of our study was to evaluate whether the main clinical/metabolic signs of DD and their clinical complications are differently distributed among Dent disease patients with different genotypes.

METHODS

Patients

DD phenotype was defined as a clinical picture characterized by an association of LMWP with hypercalciuria and/or at least one of the following: nephrocalcinosis, nephrolithiasis, phosphaturic tubulopathy, bone disorders (BDs) , chronic kidney disease (CKD) as well as family history of nephropathy.
Seventy-one unrelated patients with clinical suspicion of DD (LMWP associated with one ore more other clinical signs) were classified according to their genotypes into three groups: 1) 41 with *CLCN5* mutations (DD1); 2) 13 with *OCRL* mutations (DD2); 3) 17 without *CLCN5* and *OCRL* mutations (DD3).
The mean age of patients was 16±12 years (range 1-58 years). 48% were children, age < 14 years. All patients were males.
Three clinical/metabolic signs - LMWP, hypercalciuria, phosphaturic tubulopathy - and four consequent clinical complications - nephrocalcinosis, nephrolithiasis, BDs and CKD - were considered as present or absent in each patient.

Clinical Parameters

- LMWP was qualitatively evaluated as 24-hour urinary increased excretion of $ß_2$-microglobulin (at least five times higher than the normal value of <300 µg/day), although in some cases the increase was lower than that typical in DD.
- Hypercalciuria was defined as fasting and absolute (urinary calcium excretion >300 mg/day in adults or >4 mg per kg of bodyweight in children per day).
- Phosphaturic tubulopathy was defined as persistent hypophosphatemia in the presence of a decrease tubular reabsorption of phosphate (TRP <80%) and/or reduced renal threshold phosphate concentration ($TmPO_4/GFR$) .
- Nephrolithiasis was attributed if a stone had been passed or removed or shown in the urinary tract by X-ray or ultrasound imaging.
- Nephrocalcinosis was defined as diffuse, fine, renal parenchyma calcification on X-ray and/or ultrasound examinations.
- BDs are defined as the presence of rickets or bone demineralization. Rickets were evaluated in children during the physical and skeletal radiological examinations and bone demineralization in adults by measuring bone density of the lumbar spine and femoral neck using dual energy X-ray absorptiometry (DEXA) (T-score < -1.5 SD).
- CKD in both children and adults was attributed when creatinine clearance (CCr) was <60 ml/min/1.73 m^2 (CKD stage 3).

In all our patients parathyroid hormone (normal range 10-65 ng/l in adults and 10-55 ng/l in children) and serum calcium were normal.
None of our patients had CCr < 30 ml/min/1.73 m^2.

Statistical Analysis

- ✓ The McNemar test was used to evaluate whether two clinical signs in the same group were significantly associated.
- ✓ Fisher's exact test was used for small samples not numerically adequate for the χ^2 test.
- ✓ The χ^2 test was used to assess the variation in the frequency of the same clinical sign in two different groups to indicate the non-randomness of the difference and, therefore, the lack of homogeneity of the two classes being examined.
- ✓ The χ^2 test was also applied to evaluate the association between age and the presence of various clinical signs in each of the three groups considered.

RESULTS

The triad of symptoms (LMWP, hypercalciuria and nephrocalcinosis) was present in almost all DD1 patients indicating that the loss of ClC-5 function was the cause of clinical manifestations independently of allele heterogeneity, thus mimicking the picture shown in the *CLCN5* KO mouse models.
No association was found between age and the presence of the various signs considered in either the three group. Nephrolithiasis, however, was significantly (p=0.011) more frequent in adults than in children, but the median age of adult patients with nephrolithiasis was significantly lower in CLCN5+ than in CLCN5- groups (p=0.012).
The associations between nephrocalcinosis and nephrolithiasis, hypercalciuria and nephrolithiasis, and nephrocalcinosis and CKD were significant only in DD1 group thus suggesting a causal relationship as in *CLCN5* KO mouse models.

	Total Patients		DD1		DD2		DD3	
	N.	%	N.	%	N.	%	N.	%
Males	71		41		13		17	
Median age (years)	16± 12		14±9		13±11		18±16	
range	1-58		1-43		5-48		2-58	
LMWP	71	**100**	41	**100**	13	**100**	17	**100**
Hypercalciuria	64	**90**	40	**98®®**	12	**92**	12	**71**
Phosphaturic tubulopathy	26	**37**	13	**32**	4	**31**	9	**53**
Nephrocalcinosis	49	**69**	36	**88®**	6	**46**	7	**41**
Nepholithiasis	29	**30**	11	**27**	5	**38**	5	**29**
Bone Disorders	26	**37**	17	**41**	4	**31**	5	**29**
Kidney Failure	16	**22**	5	**12**	7	**54°**	4	**23**

® DD1 vs DD2 p=0.006 DD1 vs DD3 p=0.000 ®® DD1 vs DD3 p= 0.009 ° DD2 vs DD1 p=0.006

CONCLUSIONS

Our data indicate that the distribution of the 7 clinical signs, particularly of the 4 main complications that typically characterise DD, is different among the three genotypically different groups. This fact might indicate that although the clinical manifestations appear rather similar, the pathogenesis is different, depending on the diverse genes involved. The lack of homogeneity of clinical manifestations among the three genotypes might suggest that several genes underpin our patients' phenotypes instead of the prospected third DD gene.

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