Observations of a large Dent disease cohort

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Dent disease classically combines low-molecular-weight proteinuria, hypercalciuria with nephrocalcinosis, and renal failure. Nephrotic range proteinuria, normal calciuria, and hypokalemia have been rarely reported. It is unknown whether the changes in phenotype observed over time are explained by a decrease in glomerular filtration rate (GFR) or whether there is any phenotype-genotype relationship. To answer this we retrospectively analyzed data from 109 male patients with *CLCN5* mutations (Dent-1) and 9 patients with mutation of the *OCRL* gene (Dent-2). In Dent-1 disease, the estimated GFR decreased with age, by 1.0 to 1.6 ml/min per 1.73 m^2/yr in the absence and presence of nephrocalcinosis, respectively, with no significant difference. Median values of low-molecular-weight proteinuria were in the nephrotic range and remained at the same level even in late renal disease. End-stage renal disease occurred in 12 patients, at a median age of 40 years. Hypercalciuria decreased with glomerular filtration and was absent in 40% of the patients under 30 and 85% of those over the age of 30. Hypophosphatemia did not resolve with age and calcitriol concentrations were in the upper normal range. Kalemia decreased with age, with half of the patients over the age of 18 presenting with hypokalemia. Thus, no phenotype/genotype correlation was observed in this cohort of patients with Dent disease.

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Dent disease[1] is also known as X-linked recessive nephrolithiasis,[2] X-linked recessive hypophosphatemic rickets,[3] and idiopathic low-molecular-weight proteinuria (LMWP).[4] Affected hemizygous males have LMWP, hypercalciuria with nephrocalcinosis/nephrolithiasis, and chronic kidney disease (CKD). They present with proximal tubular defects of various severities, including hypophosphatemic rickets, proximal tubular acidosis, aminoaciduria, and renal losses of sodium, glucose, and uric acid, resulting in complete renal Fanconi syndrome (FS) in the most severe cases. Although Dent disease is often listed as a cause of

FS, its prevalence in patients with Dent disease, in whom FS has been described in few cases, is not known.[5,6] Female carriers may have a mild phenotype, including LMWP and hypercalciuria, with nephrocalcinosis or chronic renal failure developing only in very rare cases.[7,8]

Dent disease is genetically heterogeneous: 60 % of patients harbor an inactivating mutation of the chloride channel–gated 5 gene (*CLCN5*) (Dent-1, Online Mendelian Inheritance in Man 300009),[9] 15% have inactivating mutations of the inositol polyphosphate-5-phosphatase gene (*OCRL*) (Dent-2, Online Mendelian Inheritance in Man 300355),[10–12] and 25% have no mutation of these genes.[10–13]

ClC-5, the protein encoded by the *CLCN5* gene, is expressed mostly in the kidney, in the endosomes of proximal tubular cells, and to a lesser extent in medullary thick ascending limb cells and the intercalated cells of the collecting duct.[14] This widespread expression along the length of the renal tubule may account for the observed phenotypic diversity in Dent-1, extending from a purely proximal disorder to a mixture of proximal and distal disorders, including pseudo-Bartter syndrome (i.e., renal salt and potassium wasting with nephrocalcinosis)[5,15] and impaired distal acidification[8] attributed to abnormal hydrogen adenosine triphosphatase trafficking.[14,16]

We wondered whether phenotypic variations in Dent-1 reflected a genotype-phenotype correlation, the progression of CKD (i.e., nonspecific), or the natural course of the disease. We retrospectively analyzed a database of 153 families with Dent syndrome, including 61% with Dent-1, 7% with Dent-2, and 32% negative for both genes. We described the natural time course of phenotypic features in 109 affected male patients from 93 families with Dent-1 and 9 unrelated male patients with Dent-2, comparing the presentations of patients with Dent-1 and Dent-2.

RESULTS

Presentation at diagnosis

The phenotypic characteristics at clinical diagnosis of the patients with Dent-1 and Dent-2 are shown in Table 1, and mutations detected in Dent-1 families are presented in Supplementary Table S1. There were too few patients with Dent-2 for statistical analyses. However, the disease of all these patients was diagnosed before the age of 11 years, whereas that of half the patients with Dent-1 was diagnosed after the age of 11. Although the complete data set of proximal abnormalities was not available for the entire cohort, to have an idea of the prevalence of FS, we analyzed data from 70 patients for whom data for 4 or more proximal tubular abnormalities (other than LMWP and hypercalciuria) were assessed. Eight patients had at least 4 positive criteria and none negative (11%) and were classified as having complete FS. Moreover, in addition to LMWP and hypercalciuria 51 patients had 1 (17%), 2 (33%), or 3 or more (23%) proximal tubular defects (incomplete FS).

Table 1 | Presentation at clinical diagnosis of patients with Dent type 1 and type 2

	Dent-1 ($n = 108$)	Dent-2 ($n = 9$)
Age at diagnosis[a]	11 (5–21)	6 (3–8)
LMWP	93 of 93 (100%)	7 of 7 (100%)
Hypercalciuria	81 of 88 (92%)	3 of 3 (100%)
Nephrolithiasis	24 of 74 (32%)	1 of 6 (17%)
Nephrocalcinosis	44 of 104 (42%)	1 of 9 (11%)
Aminoaciduria	16 of 32 (50%)	4 of 5 (80%)
Renal hypouricemia	19 of 30 (63%)	1 of 1 (100%)
Hypokalemia	31 of 70 (44%)	1 of 4 (25%)
Glycosuria	26 of 58 (45%)	0 of 6 (0%)
Acidosis	9 of 54 (17%)	2 of 8 (25%)
Incomplete Fanconi syndrome[b]	51 of 70 (73%)	5 of 9 (55%)
Complete Fanconi syndrome[c]	8 of 70 (11%)	1 of 9 (11%)
Rickets	14 of 75 (19%)	1 of 7 (14%)
Failure to thrive	12 of 40 (30%)	4 of 6 (67%)

LMWP, low-molecular-weight proteinuria.
[a]Age at genetic diagnosis is expressed as the median [interquartile range]. Fractions are the number of positive results divided by the number of results available (%).
[b]One or more proximal tubular abnormalities (in addition to LMWP and hypercalciuria) and at least 1 negative result.
[c]At least 4 proximal tubular abnormalities of Fanconi syndrome available and all present (in addition to LMWP and hypercalciuria).

Phenotypic characteristics of patients with Dent-1

Follow-up. Median age at diagnosis was 11.5 years (interquartile range [IQR], 5.4–20.7). Only 1 visit was available in 31 patients. For the 78 others, median follow-up was 6.5 years (0.4 month to 37 years).

Growth. Growth was affected in 30% of patients, with 7 displaying severe growth retardation (i.e., height below the 2.5th percentile of the European reference). Median adult height was available for 26 European patients and was 173 cm (95% confidence interval [CI]: 155–184), which was significantly shorter than the reference values of 177 cm (95% CI of the population: 164–190, $P = 0.0065$, Wilcoxon signed rank test).

Time course of glomerular filtration rate in patients with Dent-1

Estimated GFR (eGFR) decreased with age (Figure 1a [*black circles*] and Table 2). Individual rates of decline in eGFR in patients with 5 or more visits over at least 5 years are presented in Supplementary Figure S1.

Observed and predicted ages to reach CKD stages II to V are presented in Supplementary Table S2. Twelve patients (11%) reached end-stage renal disease at a mean age of 40 years, but not all the patients at this age were at stage V CKD. This observed age was below the mean ages predicted by the linear mixed effect models for eGFR (54 years) and by the continuous-time hidden Markov model (53 years). The later estimation is consistent with observations made in the 23 subjects who were ≥30 years old at last follow-up. The observed frequency of end-stage renal disease in these subjects was 4 of 10 between 30 and 40 years, 3 of 9 in subjects between 40 and 50 years, and 3 of 4 in those between 50 and 60.

Nephrocalcinosis was present at clinical diagnosis in 44 patients and occurred during follow-up in 18 patients