Urol Res (2006) 34: 61–63
DOI 10.1007/s00240-005-0005-5

CASE REPORT

F. Anglani · P. Bernich · E. Tosetto · M. Cara
A. Lupo · F. Nalesso · A. D'Angelo · G. Gambaro

Family history may be misleading in the diagnosis of Dent's disease

Received: 2 July 2005 / Accepted: 14 November 2005 / Published online: 14 January 2006

Abstract The rare Dent's disease manifests with medullary nephrocalcinosis, nephrolithiasis, hypercalciuria, low molecular weight proteinuria and other tubular dysfunctions, rickets or osteomalacia, and renal failure, in various combinations. It is a recessive X-linked condition. Clinicians consider family history a fundamental pointer to its diagnosis, but this is not invariably the case as clearly pointed out by the two reported cases.

Keywords Rickets · Renal stone · Hypercalciuria · Nephrocalcinosis · X-linked nephrolithiasis · Dent's disease

Case report 1

SP is a 28-year-old male, with a BW of 53 kg and 153 cm tall; his estimated creatinine clearance is 37 ml/min/1.73 m^2.

When he was 18 months old, short stature and genu varum were recorded, together with proteinuria and glucosuria.

At the age of 32 months, his BW and height were below the 10th and 3rd percentiles, respectively. He had abnormal aminoaciduria, glucosuria (5,533 μmol/l), proteinuria (2 g/l), hypercalciuria (0.3 mmol/kg BW), hypophosphatemia (0.84 mmol/l), and hypobicarbonatemia (14 mmol/l); serum creatinine was normal (44.2 μmol/l). The diagnosis of nutritional rickets was suggested and he was treated with oral vitamin D, neutral phosphate, and bicarbonate.

At 5 years of age, there was no further evidence of metabolic acidosis, glucosuria, or aminoaciduria, while calciuria and proteinuria were still abnormal. The diagnosis of hypophosphatemic rickets with hypercalciuria (VDRRH) was advanced and treatment with thiazides was initiated.

At 8 years of age, medullary nephrocalcinosis was discovered after an episode of gross hematuria. Serum creatinine was 70.7 μmol/l, and rose to 88.4 μmol/l at 12 years of age and 132.6 μmol/l at 18 years of age, when urinary protein electrophoresis showed an abnormal low molecular weight (LMW) protein absorption pattern.

There is reportedly no renal disease in his family pedigree (Fig. 1). One paternal blood relative and the maternal great-grandfather have short stature, and the maternal grandmother had renal stones. There is no consanguinity between the two arms, and no kidney or bone disorders are described in his first-degree relatives.

Although the clinical presentation and evolution were suggestive of DD, said diagnosis was judged unlikely because the inheritance pattern pointed to an autosomal vitamin D dependent rickets with hypercalciuria, which has indeed been described [1].

Molecular analysis of the *CLCN5* gene was nonetheless performed, screening all the coding sequences (exons 2–12) and the exon–intron boundaries of *CLCN5* gene using SSCP analysis and direct PCR product sequencing, as recently described [2]. A nucleotide C–T substitution in exon 7 at position 1,022 (1,022 C > T) was identified. This nucleotide substitution leads to the non-conservative serine → leucine substitution (S244L). Such a mutation has been already reported. The variant was inherited from the mother who disclosed increased excretion of β_2-microglobulin.

F. Anglani · E. Tosetto
Department of Medical and Surgical Sciences, Laboratory of Molecular Biology, University of Padova, Padova, Italy

F. Nalesso · A. D'Angelo
Nephrology Division, Department of Medical and Surgical Sciences, University of Padova, Padova, Italy

M. Cara
Nephrology Unit, General Hospital, Camposampiero (PD), Italy

P. Bernich · A. Lupo · G. Gambaro (✉)
Department of Biomedical and Surgical Sciences, Nephrology Division, University of Verona, Ospedale Maggiore, P.le Stefani 1, 37126 Verona, Italy
E-mail: giovanni.gambaro@univr.it
Tel.: +39-045-8072521
Fax: +39-045-915176

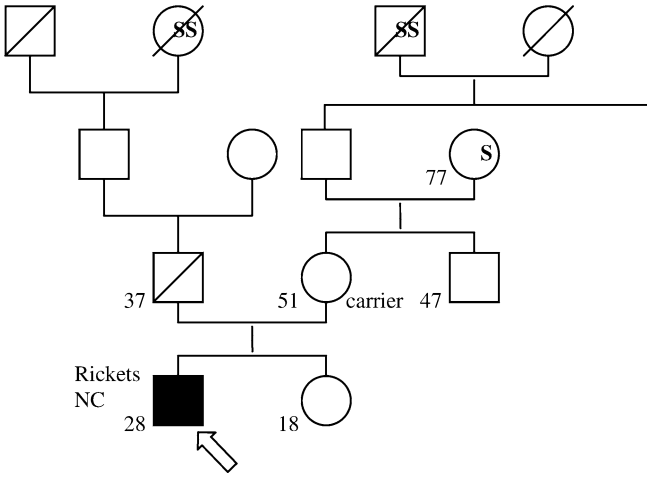

Fig. 1 Case 1's family pedigree. *SS* short stature, *S* renal stone, *NC* nephrocalcinosis, *arrow* proband, *full black symbol* mutated individual, *crossed symbol* dead individual. The clinical phenotypes SS or rickets affect both genders (apparently ruling out an X-linked disorder, and thus pointing to a autosomic condition; since these phenotypes are not described in two generations, this suggests a recessive autosomic trait). Same conclusion if NC and S are considered as different expression of the same genetical disorder

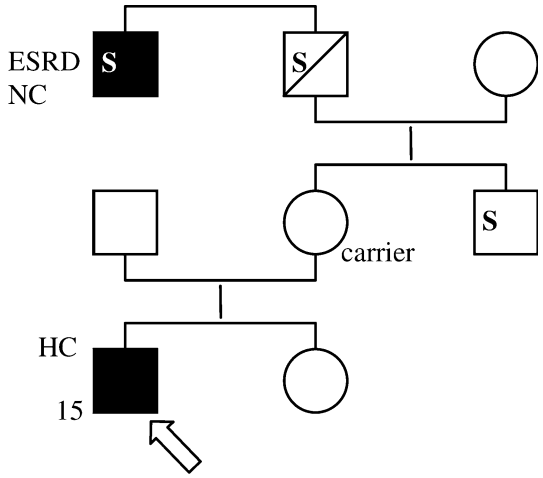

Fig. 2 Case 2's family pedigree. *S* renal stone, *NC* nephrocalcinosis, *HC* hypercalciuria, *arrow* proband, *full black symbol* mutated individuals, *crossed symbol* dead individual. By considering NC, S and HC as different signs of the same genetical disorder, since all generations are affected, an autosomic dominant disorder (with incomplete penetrance in consideration that the proband's mother is healthy) might be suggested

Case report 2

BA is a 15-year-old boy who has been followed up regularly for a year now due to a chance discovery of microhematuria and mild proteinuria (0.8–1.0 g/24 h) at a sports medical check-up. His BW is 65 kg and he is 175 cm tall and otherwise normal; his personal history is irrelevant. His family history suggested a dominant autosomal transmission of stone-related conditions, since the grandfather and an uncle on the mother's side were renal stone formers, and a great uncle has end-stage renal disease (ESRD) with a history of renal stones and a nephrocalcinosis disorder labeled as medullary sponge kidney (Fig. 2).

Serum creatinine is 45.1 μmol/l. Immunological serum indices (complement, immunoglobulins, immunocomplexes, rheumatoid factor, anti-nucleus, and DNA antibodies) are all normal, as are audiometric and renal US test results. Given the finding of calcium oxalate crystals in his urine, oxaluria and calciuria were tested and hypercalciuria (16.4 mmol/24 h) was detected. A urine protein selectivity index of 0.64 prompted the suspicion of a glomerular disease, however, so a renal biopsy was performed.

Optical microscopy disclosed numerous glomeruli, all normal except two, which were hyaline. Patchy interstitial fibrosis was observed, associated with cellular infiltrates in one area. Non-specific segmental or diffuse mesangial deposition of IgM and C3 was seen in some glomeruli. Electron microscopy showed normal GBM. On the whole, the picture suggested a non-immunological interstitial disorder. The finding of concomitant hypercalciuria prompted von Kossa staining to rule out DD and a sample of the patient's DNA was requested for the referring nephrologist.

While the former ruled out any tissue calcifications, molecular analysis on the *CLCN5* gene identified a nucleotide G to T substitution in exon 7 in position 1,070 (1,070 C > T), leading to the non-conservative glycine → valine substitution (G260V). This is a *CLCN5* gene mutation never hitherto described. It was also found in the mother and in the ESRD uncle. The mother had abnormal urinary levels of β_2-microglobulin.

Discussion

Dent's disease (DD) is characterized by medullary nephrocalcinosis, nephrolithiasis, hypercalciuria, LMW proteinuria and other tubular dysfunctions, rickets or osteomalacia, and renal failure, in various combinations [3]. This rare disease presents in childhood or early adult life. Females are only exceptionally affected [3] because it is a recessive X-linked condition caused by mutations in the chloride channel *CLCN5* gene [4, 5], located on the short arm of the X chromosome (Xp11.22) [6]. This gene encodes a 746-amino acid protein expressed in the renal proximal tubules, the thick ascending loop of Henle, and α-intercalated cells of the collecting ducts [7, 8], which has a role in endosomal acidification processes. A defect in endosomal-dependent phenomena, i.e. in renal proximal tubule LMW protein absorption and receptor trafficking, appears to be the pathophysiological culprit for the disease [9].

Clinicians quite often consider family history a relevant, possibly even fundamental pointer to the diagnosis of DD, but this is not invariably the case since puzzling

inheritance patterns may certainly be the consequence of the DD composite phenotype, and the fact that some DD manifestations are widespread clinical problems. The two case reports depict misleading inheritance patterns.

They are characterized by a family history apparently without the X-linked inheritance typical of DD. The inheritance pattern suggested a recessive autosomal transmission of the short stature rickets in the first case and a dominant one of the stone disease in the second. The clinical diagnosis of DD can prove difficult because the clinical picture may be very vague or non-specific, possibly flawed by recall bias (e.g. the short stature in case 1's family), or purely biochemical (hypercalciuria, LMW proteinuria, i.e. two findings demanding non-routine analyses even in the nephrological setting). Cases may even present with hypercalciuria alone, with none of the other features of the disease [10], or with ESRD without nephrocalcinosis [3], or with seemingly idiopathic calcium nephrolithiasis. That is why some cases can go unrecognized, preventing the recognition of an inherited pattern and particularly of a clear X-linked transmission. This is even more likely in the small family units now typical of western countries.

On the other hand, one of the main signs of DD, i.e., calcium renal stones, is very common in the general population (the prevalence of idiopathic calcium nephrolithiasis is as high as 10%), so it may be that calcium nephrolithiasis, in its idiopathic form, is a chance occurrence in DD families (as in one member of each of the two families), giving rise to atypical, confounding inheritance patterns.

The message in this paper is that a diagnosis of DD is suggested primarily by a patient's clinical signs, while the familial transmission pattern is not necessarily a feature. While the presence of an X-linked inheritance pattern supports the diagnosis of DD, its absence by no means suffices to rule out the disorder. The finding that probands' mothers have LMW proteinuria is a strong hint to the diagnosis of DD. Actually both probands' mothers had abnormal urinary excretion of β_2-microglobulin. Thus, in accordance with the literature [11], we believe that assaying LMW proteinuria (or β_2-microglobulin, α_1-microglobulin, or retinol-binding protein) in first-degree female relatives of suspected cases is a valuable diagnostic tool before searching for *CLCN5* gene mutations or mutations of the OCRL1 gene which has been recently reported as causing an X-linked disorder similar to DD [12]. On the contrary, LMW proteinuria is not found in first-degree female carriers of conditions mimicking DD, such as autosomal recessive proximal tubulopathy with hypercalciuria [13].

References

1. Godefroid N, Proesmans W (2003) A girl with rickets and nephrocalcinosis. Pediatr Nephrol 18:573
2. Tosetto E, Graziotto R, Artifoni L, Nachtigal J, Cascone C, Conz P, Piva M, Dell'Aquila R, De Paoli Vitali E, Citron L, Nalesso F, Antonello A, Vertolli U, Zagatti R, Lupo A, D'Angelo A, Anglani F, Gambaro G (2005) Dent's disease and prevalence of renal stones in dialysis patients in north-eastern italy. J Human Genet (in press)
3. Wrong OM, Norden AGW, Feest TG (1994) Dent's disease; a familial proximal renal tubular syndrome with low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease, progressive renal failure and a marked male predominance. Q J Med 84:473
4. Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, Harding B, Bolino A, Devoto M, Goodyer P, Rigden SP, Wrong O, Jentsch TJ, Craig IW, Thakker RV (1996) A common molecular basis for three inherited kidney stone diseases. Nature 379:445
5. Thakker RV (2000) Pathogenesis of Dent's disease and related syndromes of X-linked nephrolithiasis. Kidney Int 57:787
6. Scheinman SJ, Pook MA, Wooding C, Pang JT, Frymoyer PA, Thakker RV (1993) Mapping the gene causing X-linked recessive nephrolithiasis to Xp11.22 by linkage studies. J Clin Invest 91:2351
7. Gunther W, Luchow A, Cluzeaud F, Vandewalle A, Jentsch TJ (1998) ClC-5, the chloride channel mutated in Dent's disease, colocalizes with the proton pump in endocytically active kidney cells. Proc Natl Acad Sci USA 95:8075
8. Devuyst O, Christie PT, Courtoy PJ, Beauwens R, Thakker RV (1999) Intra-renal and subcellular distribution of the human chloride channel, ClC-5, reveals a pathophysiological basis for Dent's disease. Hum Mol Genet 8:247
9. Piwon N, Gunther W, Schwake M, Bosl MR, Jentsch TJ (2000) ClC-5 Cl^--channel disruption impairs endocytosis in a mouse model for Dent's disease. Nature 408:369
10. Scheinman SJ, Cox JP, Lloyd SE, Pearce SH, Salenger PV, Hoopes RR, Bushinsky DA, Wrong O, Asplin JR, Langman CB, Norden AG, Thakker RV (2000) Isolated hypercalciuria with mutation in CLCN5: relevance to idiopathic hypercalciuria. Kidney Int 57:232
11. Reinhart SC, Norden AG, Lapsley M, Thakker RV, Pang J, Moses AM, Frymoyer PA, Favus MJ, Hoepner JA, Scheinman SJ (1995) Characterization of carrier females and affected males with X-linked recessive nephrolithiasis. J Am Soc Nephrol 5:1451
12. Hoopes RR Jr, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus J, Simckes A, Tasic V, Toenshoff B, Suchy SF, Nussbaum RL, Scheinman SJ (2005) Dent Disease with mutations in OCRL1. Am J Hum Genet 76:260
13. Magen D, Adler L, Mandel H, Efrati E, Zelikovic I (2004) Autosomal recessive renal proximal tubulopathy and hypercalciuria: a new syndrome. Am J Kidney Dis 43:600