North Bengal Medical College Journal
Vol 2 No 2 July 2016

Case Report

Dent's Disease: A Rare X-linked Kidney Disease

Salma Jahan,[1] Khaza Habib Salim,[2] Ferdous Jahan,[3] Md.Saiful Islam[4]

Revised : January 09, 2016 Accepted : January 23, 2016

Abstract

Dent's disease is a rare X-linked recessive proximal tubulopathy. It is typically characterized by low-molecular-weight (LMW) proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, hypophosphatemia, rickets and slowly progressive renal failure. The laboratory and clinical features may occur in various combinations. The early diagnosis of Dent's disease is often problematic because affected children may have mild clinical and biochemical signs, detecting LMW proteinurea is not available in many laboratories, and genetic results are not clear in all cases. We report on a four months old boy with nephrocalcinosis having one sister and a brother died earlier of same disease process.

Key words: *Dent's disease, Nephrocalcinosis, Proximal tubulopathy*

North Bengal Med. Coll.J. 2016; 2 (2) : 63-69

1. *Senior Consultant of Paediatrics, Centre for Woman and Child Health, Ashulia, Dhaka*
2. *Assistant Professor of Paediatric Surgery, Shaheed TajuddinAhmed Medical College, Gazipur*
3. *Medical Officer, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka*
4. *Associate Professor of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka*

Correspondence *Salma Jahan, Email: sjshally@yahoo.com*

Introduction

Genetic basis of nephrocalcinosis and renal failure is suspected when number of cases cluster occur in a family. The intention of this case report arises when three sibling of a same family died with same kind of kidney disease. With all limitations of investigations and treatment facilities in our centre, we provisionally diagnosed the case as Dent's Disease for further discussion and attention.

Dent's disease is now the generally accepted name for a group of X-linked renal tubular disorders, including X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low-molecular weight (LMW) proteinurea.[1–3] Dent's disease is caused mainly by mutations in the CLCN5 gene (Dent's disease 1) located on chromosome Xp11.22, which encodes for the 746amino-acid ClC-5 chloride channel implicated in the tubular endocytoticabsorption of albumin and LMW proteins. ClC-5 was first thought to provide a shunt conductance in early endosomes, enabling efficient intraluminal acidification by V-type H + ATPase.[4–6]It has recently beendemonstrated, however, that ClC-5 functions as a Cl^-/H^+antiporter when activated by positive voltages.[7,8] No CLCN5 gene mutations are detected in approximately 40% of patients with the classic symptoms of Dent's disease, suggesting a locus heterogeneity. The OCRL gene located on chromosome Xq26.1, whose mutations cause Lowe syndrome, has recently been found altered in 20% Dent's patients,[9] but about 20% of patients carry neither CLCN5 nor OCRL mutations[10–13]. Dent's disease tends to become manifest in childhood or early adult life. It is characterized by LMW proteinuria, hypercalciuria, medullary nephrocalcinosis, nephrolithiasis, other tubular dysfunctions, and renal failure in various combinations. Different groups of researchershave recently reported on case series of patients with atypical or rare Dent,s disease 1 phenotypic signs, such as episodeic night blindness,[14] Bartter-like syndrome,[15,16] growth hormone deficiency,[17] and proteinuria with histological evidence of focal segmental glomerulosclerosis.[18,19] Dent's disease patients carrying OCRL gene mutations (Dent's disease 2) have none of the classic symptoms accompanying renal tubulopathy in Lowe syndrome, that is mental retardation, bone disease, growth retardation, congenital cataracts, delayed motor milestones. This milder phenotype is not attributable to less severe changes in protein expression or enzyme activity, as both are significantly reduced or absent.[10–13] The renal symptoms of Lowe syndrome are very similar to those of Dent's disease, though the characteristics of the patients' tubular dysfunction may differ. Recently however, two different OCRL mutations each causing both Dent's disease 2 and Lowe syndrome even in the same family have been described.[20] In short, Dent's disease seems to be characterized by a genetic and phenotypic heterogeneity. A few

studies were reported regarding Dent's disease.

Here, we have discussed an atypical case of nephrocalcinosisinvolving a syndromic variant of Dent's disease, without documented CLCN5 and OCRL mutations.

The Case

A male baby of 4months with fever, vomiting, with frequency of urination and progressive loss of weight was referred to Centre for Women and Child Health Hospital, Ashulia, Dhaka, for evaluation and better management. The full term healthy male boy with 2.9 kg weight delivered with Lower uterine Caesarean section (LUCS). From the12 days of age, he had intermittent fevers and recurrent urinary tract infection with failures to gain weight. On admission, his body weight was measured 3.2 kg, and height 52 cm.His BP was recorded as 70/50 mm Hg. He was malnourished, anaemic, mild peripheral edema with normal cardio-respiratory examination; and no rashes or arthritis. The abdomen was soft and non tender. The liver was not enlarged, and the spleen was palpable two finger breadths below the costal margin. He had low grade fever, severe dehydration with respiratory distress and was managed accordingly with intravenous fluid and antibiotics. But the patient was died on 3rd days of admission. His urine analysis shows proteinuria, plenty of pus cells with no growth of microorganism on urine culture. He had 2.1 mg/dl of serum creatinine, 8.6 mg/dl of serum calcium, 5.5 mmol/l of serum potassium, and normal serum inorganic phosphate. His complete blood count showed 8.8 gm/dl Hb, raised ESR and leukocytosis. Renal ultrasonography showed, both the kidneys were enlarged in size (right kidney was 4.5 cm, left kidney was 5.0 cm), but normal in shape and position. Cortico-medullary differentiation was well, pelvicalyceal system were not dilated. Multiple echogenic structures seen at both kidneys which were arranged radially with feature of nephrocalcinosis. (Figure 1)

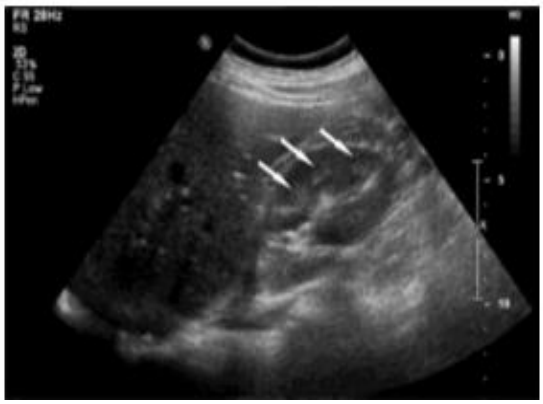

Figure 1: Ultrasound of the Right Kidney

Family history revealed that parents of the patient were maternal cousin. They were two brothers and one sister. His older brother died at the age of 5 months due to CKD with nephrocalcinosis. His elder sister died at the age of 1 year with progressive microalbuminuria, hyperkalemia and medu-llary nephrocalcinosis.

Renal biopsy of brother or sister shows mild focal global glomerulosclerosis, tubular atrophy, and interstitial fibrosis with multiple medullary tubular calcifications, consistent with Dent's disease. Gene analysis was not done due to short survival and non-availability of test facility.

Discussion

Dent's disease is a rare recessive X-linked renal tubular disorder manifesting byFanconi's syndrome or proximal tubular dysfunction of different grades, nephro-lithiasis, nephrocalcinosis, rickets and slowly progressive renalfailure. Its precise prevalence is unknown and approximately 250 affected families were reported worldwide. In the past, several phenotypic variants of Dent's disease were independently described and named as separate disorders, including X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemicrickets and familial idiopathic LMW proteinuria with hypercalcinuria in Japanese patients.[21] Mutations in the CLCN5 gene encoding the electrogenic chloride/proton exchanger CIC-5 participating in the receptor-mediated endocytosis in the proximal tubule are a causative factor for Dent's disease type 1. Large number of different mutations in this gene was identified, until now, but no clear genotype-phenotype correlation was found. Dent's disease type 1 is characterized by symptoms exclusively related to proximal tubular dysfunction. Dent's disease of type 2 is thought to be a mild variant of oculocerebrorenal syndrome (Lowe syndrome) because both conditions are caused by mutation in the OCRL1 gene and therefore, the former is manifested sometimes with extrarenal features, including mild ocular involvement, mild intellectual disability, muscle hypotonia, umbilical hernia or short stature.[21,22]

Due to the mode of inheritance, Dent's disease affects primarily males. Female carriers remain predominantly asympto-matic, although they may have mild proteinuria and/or hypercalciuria.[22,23] The parents of our patient were cousins, and the mode of inheritance was not determined, due to lack of facility. The clinical features of Dent's disease are often subtle with the majority of patients being asymptomatic during infancy and early childhood. Initial symptoms may be variable and non-specific, including polyuria, proteinuria, microscopic haematuria or renal colic due to urolithiasis. Growth retardation may be present,[22]and that was observed in our patient. Proteinuria resulted from impaired reabsorption of proteins in proximal tubules is a typical and constant feature of Dent's disease and consists mainly of different LMW-proteins, including alpha-1- and beta-2-micro-globulin, cystatin C, lysozyme, retinol-binding protein (RBP), vitamin-D-binding protein and trace amounts of albumins.[22] Urinary protein excretion in patients with Dent's disease is usually moderate and only in rare cases of coexisting focal segmental

glomerulosclerosis reaches the nephrotic range.[19] Hypercalcinuria of different severity affects approximately 90% of patients. Urinary calcium excretion is usually higher in children than in adults, because calcinuria tapers with decreasing renal function.[22] Nephrocalcinosis is an important feature of Dent's disease affecting approximately 75% of patients.[22] It may serve as a cardinal feature for diagnosis. Nephrolithiasis is observed less commonly, and stones usually consist of calcium phosphate or calcium oxalate,[22]which was observed in our case. Hypercalciuria is thought to be a main aetiological factor of nephrocalcinosis and urolithiasis because urinary oxalate and citrate excretion is usually normal.We could not perform the 99mTc-DMSA renal scanning due to lack of facility in our hospital. In most children with Dent's disease, renal function is normal, but unfortunately, it declines during adulthood. The pathogenesis of this process is still unclear. But 30 to 80% of affected patients progress to end stage renal failure in the third to fifth decade of life.[23] The increased activation of PTH receptors on the apical membrane of the proximal tubule by excreted PTH may cause urinary phosphate loss, hypophosphatemia and rickets in a minority of patients.[24] Patients with Dent's disease show a poor accumulation of 99mTc-DMSA in renal parenchyma and rapid excretion of radiotracer due to proximal tubular endocytic dysfunction.[25] Some patients develop recurrent episodes of nocturnal blindness, probably due to renal loses of RBP. They are responsive to vitamin A therapy.[26] Currently, there is no definite strategy for the management of Dent's disease and recommended treatment will be mostly supportive. Thiazide diuretics and dietary salt restriction are used to reduce calciuria and to prevent the occurrence of nephrocalcinosis and nephrolithiasis. ACE inhibitors may be useful to reduce glomerular component of proteinuria. In recent animal studies a high-citrate diet seems to delay the progression of renal failure.[26] In future, more studies will be required for both diagnosis and management purpose.

Conclusion

In this study, we were confined with in the clinical features and conventional investigations. Most recent investigations such as genetic evaluation and renal biopsy will be required for final diagnosis. More studies are to be expected for further evaluation regarding Dent's disease.

References

1. Wrong OM, Nordern AGW, Feest TG. Dent's disease: a familial renal tubular syndrome with hypercalcinuria, tubular proteinuria, rickets, nephrocalcinosis and eventual renal failure. Q J Med. 1990;77: 1086–1087.

2. Lloyd SE, Pearce SHS, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ et al. A common molecular basis for three inherited kidney stone diseases. Nature. 1996;379: 445–449.
3. Thakker RV. Pathogenesis of Dent's disease and related syndromes of X-linked nephrolithiasis. Kidney Int. 2000;57: 787–793.
4. Gunther W, Luchow A, Cluzeaud F, Vandewalle A, Jentsch TJ. ClC-5, the chloride channel mutated in Dent's disease, colocalizes with the proton pump in endocytotically active kidney cells. Proc Natl AcadSci USA. 1998;95: 8075–8080.
5. Devuyst O, Christie PT, Courtoy PJ, Beauwens R, Thakker RV. Intra-renal and sub cellular distribution of the human chloride channel, CLC-5 reveals a pathophysiological basis for Dent's disease. Hum Mol Genet. 1999;8: 247–257.
6. Hara-Chikuma M, Wang Y, Guggino SE, Guggino WB, Verkman AS. Impaired acidification in early endosomes of ClC-5 deficient proximal tubule. Biochem Biophys Res Commun. 2005; 329: 941–946.
7. Picollo A, Pusch M. Chloride/proton antiporter activity of mammalian CLC proteins ClC-4 and ClC-5. Nature. 2005;436: 420–423.
8. Scheel O, Zdebik AA, Lourdel S, Jentsch TJ. Voltage-dependent electro-genic chloride/ proton exchange by endosomal CLC proteins. Nature. 2005;436: 424–427.
9. Hoopes Jr RR, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus Jet al. Dent Disease with mutations in OCRL1. Am J Hum Genet. 2005;76: 260–267.
10. Shrimpton AE, Hoopes Jr RR, Knohl SJ, Hueber P, Reed AA, Christie PT et al. OCRL1 mutations in Dent 2 patients suggest a mechanism for phenotypic variability. Nephron Physiol. 2009;112: 27–36.
11. Cho HY, Lee BH, Choi HJ, Ha IS, Choi Y, Cheong HI. Renal manifestations of Dent disease and Lowe syndrome. Pediatr Nephrol. 2008;23: 243–249.
12. Sekine T, Nou K, Iyengar R, Xue Jun Fu, Matsuo M, Tanaka Ret al. OCRL1 mutations in patients with Dent disease phenotype in Japan. Pediatr Nephrol. 2007;22: 975–980.
13. Utsch B, Bo ¨kenkamp A, Benz MR, Besbas N, Dötsch J, Franke I et al. Novel OCRL1 mutations in patients with the phenotype of Dent disease. Am J Kidney Dis. 2006;48: e1– e14.
14. Sethi SK, Ludwig M, Kabra M, Hari P, Bagga A. Vitamin A responsive night blindness in Dent's disease. Pediatr Nephrol. 2009;24: 1765–1770.
15. Bogdanovic ´ R, Draaken M, Toroman-ovic ´ A, Dordevic ´ M, Stajic ´ N, Ludwig M: A novel CLCN5 mutation in a boy with Bartter-like syndrome and partial growth hormone deficiency. Pediatr Nephrol. 2010;25: 2363–2368.

16. Besbas N, Ozaltin F, Jeck N, Seyberth H, Ludwig M. CLCN5 mutation (R347X) associated with hypokalaemic metabolic alkalosis in a Turkish child: an unusual presentation of Dent's disease. Nephrol Dial Transplant. 2005;20: 1476–1479.
17. Sheffer-Babila S, Chandra M, Speiser PW. Growth hormone improves growth rate and preserves renal function in Dent disease. J Pediatr Endocrinol Metab. 2008;21: 279–286.
18. Copelovitch L, Nash MA, Kaplan BS. Hypothesis: Dent disease is an under recognized cause of focal glomerulosclerosis. Clin J Am Soc Nephrol. 2007;2: 914–918.
19. Frishberg Y, Dinour D, Belostotsky R, Becker-Cohen R, Rinat C, Feinstein S et al. Dent's disease manifesting as focal glomerulosclerosis: Is it the tip of the iceberg? Pediatr Nephrol. 2009;24: 2369–2373.
20. Hichri H, Rendu J, Monnier N, Coutton C, Dorseuil O, Poussou RV et al. From Lowe syndrome to Dent disease: correlations between mutations of the OCRL1 gene and clinical and biochemical phenotypes. Hum Mutat. 2011;32: 379–388.
21. Sahay M. Diseases of Renal Parenchyma. In Tech. Rijeka (Croatia): Dent's disease ; p.17-32.
22. Bockenhauer D, Bokenkamp A, Nuutinen M, Unwin Rvan't, Hoff W, Sirimanna T et al. Novel OCRL mutations in patients with Dent-2 disease. J Pediat Genet. 2012;1: 15-23.
23. Claverie-Martin F, Ramos-Trujillo E, Garcia Nieto V. Dent's disease: clinical features and molecular basis. Pediatr Nephrol. 2011;26(5): 693-704.
24. Amnigeri RA, Rajagopalan R. Hypophosphatemic rickets due to Dent's disease: A case report and review of literature. Indian J Nephrol. 2009;19(4): 163-166.
25. Weyer K, Nielsen R, Petersen SV, Christensen EI, Rehling M, Birm H. Renal Uptake of 99mTc-Dimercaptosuccinic Acid Is Dependent on Normal Proximal Tubule Receptor-Mediated Endocytosis. J Nucl Med. 2012;54(1): 1-7.
26. Becker-Cohen R, Rinat CH, Ben-Shalom E, Feinstein S, Ivgi H, Frishberg V. Vitamin A deficiency associated with urinary retinol binding protein wasting in Dent's disease. Pediatr Nephrol. 2012;27(7): 1097-1102.