A case of adult Dent disease in Japan with advanced chronic kidney disease

Ken Saida · Yuji Kamijo · Daisuke Matsuoka · Shunsuke Noda · Yoshihiko Hidaka ·
Tetsuo Mori · Hisashi Shimojo · Takashi Ehara · Kenichiro Miura ·
Junko Takita · Takashi Sekine · Takashi Igarashi · Kenichi Koike

Received: 18 February 2013 / Accepted: 21 October 2013 / Published online: 2 November 2013
© Japanese Society of Nephrology 2013

Abstract Dent disease is an inherited tubulopathy caused by a mutation in the *CLCN5* chloride channel gene. In cases of Dent disease in Japan (Japanese Dent, J-Dent), renal function is generally preserved and rarely progresses to advanced kidney dysfunction. However, the long-term prognosis of J-Dent remains unknown. We report the case of a 32-year-old man with J-Dent who developed advanced kidney dysfunction. Since the age of 3 years, he persistently exhibited proteinuria, and

examination of a kidney biopsy specimen indicated focal segmental glomerulosclerosis (FSGS)-like lesions. Repeated corticosteroid treatments were found to be ineffective. After the age of 18 years, the patient was lost to follow-up and treatment was discontinued. The patient presented to our hospital again at the age of 32 years with advanced kidney dysfunction with low-molecular-weight proteinuria (LMWP), along with proximal tubular dysfunction and nephrocalcinosis. The patient's 5-year-old nephew was also found to have LMWP from the age of 7 months. Therefore, Dent disease was suspected and genetic testing in the patient and his nephew revealed a *CLCN5* mutation. Our case report suggests that J-Dent may cause advanced kidney dysfunction in adulthood, and, therefore, close collaboration between pediatricians and nephrologists is essential for the early identification of this complication. When male patients exhibit chronic kidney disease (CKD) of unknown etiology along with proximal tubular dysfunction and nephrocalcinosis, Dent disease should be considered. Investigations of undiagnosed adult J-Dent cases and further research on the natural history of J-Dent will help us better understand its clinical characteristics, prognosis, and effective treatment options.

K. Saida · D. Matsuoka · S. Noda · Y. Hidaka · K. Koike
Department of Pediatrics, Shinshu University School of
Medicine, 3-1-1 Asahi, Matsumoto, Nagano, Japan

Y. Kamijo (✉)
Department of Nephrology, Shinshu University School of
Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
e-mail: yujibeat@shinshu-u.ac.jp

T. Mori
Department of Pediatrics, Shinshu Ueda Medical Center,
1-27-21 Midorigaoka, Ueda, Nagano, Japan

H. Shimojo · T. Ehara
Department of Pathology, Shinshu University School of
Medicine, Nagano, Japan

K. Miura · J. Takita · T. Igarashi
Department of Pediatrics, Graduate School of Medicine, The
University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

J. Takita
Department of Cell Therapy and Transplantation Medicine,
Graduate School of Medicine, The University of Tokyo, Tokyo,
Japan

T. Sekine
Department of Pediatrics, Toho University School of Medicine,
Ohashi Hospital, 2-17-6 Ohashi, Meguro-ku, Tokyo, Japan

Keywords *CLCN5* · Dent disease · Focal segmental
glomerulosclerosis · Japanese Dent (J-Dent) ·
Low-molecular-weight proteinuria (LMWP)

Abbreviations

LMWP	Low-molecular-weight proteinuria
XRN	X-linked recessive nephrolithiasis
XLHR	X-linked recessive hypophosphatemic rickets
FSGS	Focal segmental glomerulosclerosis

Introduction

Dent disease is an inherited proximal tubulopathy characterized by low-molecular-weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis, and nephrolithiasis. The onset of clinical symptoms can vary between patients; therefore, making a definitive diagnosis is difficult, particularly during the early stages of Dent disease [1]. Genetic mutations of *CLCN5* and *OCRL* account for 60 % and 15 % of all Dent disease cases, respectively. Although more than 80 distinct *CLCN5* mutations have been associated with Dent disease, no genotype–phenotype correlations have been identified, even within the same family [2].

Prior to the identification of these genetic mutations, Dent disease had often been categorized into 4 types according to geographical location, clinical manifestations, and/or prognosis: Dent disease in the UK, X-linked recessive nephrolithiasis (XRN) in North America, X-linked recessive hypophosphatemic rickets (XLHR) in Europe, and Dent disease in Japan (J-Dent). Compared to the other types, renal function in J-Dent has been reported to be relatively well preserved and rarely progresses to advanced kidney dysfunction [3, 4]. However, the long-term prognosis of J-Dent remains unknown. In this case report, we describe the case of a 32-year-old man with J-Dent who developed advanced kidney dysfunction.

Case report

A 32-year-old man presented to our hospital with proteinuria and kidney dysfunction that were detected during a routine medical examination. The presence of proteinuria in this patient was first noted at the age of 3 years; thereafter, persistent elevated levels of urinary protein were detected. He did not exhibit any abnormal findings on physical examination, and the laboratory findings, including those of chemical or immunoassay analysis, were found to be normal, except for the presence of proteinuria. In addition, no kidney malformations, growth abnormalities, or intellectual disabilities were noted in the patient. He did not have any history of taking any drugs or exposure to heavy metals that may potentially be associated with kidney toxicity. A kidney biopsy was performed at the age of 6 years. The pathological record information at that time indicated that the patient was diagnosed with focal segmental glomerulosclerosis (FSGS); however, those kidney biopsy specimens were not stored for subsequent examination. Despite 2 years of treatment with steroids, the patient continued to exhibit proteinuria. As the serum creatinine level gradually increased, a second kidney biopsy was performed at the age of 14 years (Fig. 1). The second kidney biopsy specimens did not exhibit typical

Fig. 1 Light microscopic analysis of kidney biopsy specimens obtained at the age of 14 years. Kidney sections were stained with H&E. Progression of glomerulosclerosis as well as tubular atrophy and dilatation were detected

FSGS lesions; however, we noted the presence of several normal glomeruli, as well as many areas of global glomerulosclerosis with tubular atrophy and dilatation. These findings were suspected to be related to the initial diagnosis of FSGS, although the final diagnosis was not confirmed. In the second biopsy specimens, no calcification was noted. The patient again underwent steroid therapy, but the proteinuria remained refractory to this treatment. The patient continued to undergo treatment until the age of 18 years, at which time he stopped visiting the hospital clinics and discontinued the steroid treatments, as he moved to another prefecture. Routine medical examinations repeatedly detected proteinuria and exacerbation of kidney dysfunction at the age of 24 and 26 years, but the patient did not visit the hospital again until the age of 32 years.

The patient's height and weight were 160 cm [−1.9 standard deviations (SD)] and 52 kg, respectively. Blood pressure was normal at 120/86 mmHg. He did not exhibit any symptoms associated with kidney dysfunction, such as edema. Laboratory investigations indicated no evidence of anemia, acidosis, or serum electrolyte abnormalities, but they showed high levels of serum creatinine and intact parathyroid hormone, suggesting kidney dysfunction and secondary hyperparathyroidism (Table 1). Urinalysis, urine chemistries, and urine protein electrophoresis indicated marked elevations in the levels of LMWP (α_1 -microglobulin and β_2 -microglobulin), as well as albuminuria (Table 1; Fig. 2). Moreover, urine analyses showed hyposmotic urine, glucosuria without hyperglycemia, panaminoaciduria (data not shown), and decreased % tubular reabsorption of phosphate, suggesting apparent dysfunction in proximal tubular reabsorption (Fanconi syndrome). The transtubular potassium concentration gradient was normal, indicating relatively preserved distal tubular function.

Table 1 Laboratory investigation

Table 1 Laboratory investigation	Serum chemistries		Urinalysis	
	Total protein	7.4 g/dL	pH	7.5
	Albumin	4.6 g/dL	Urine specific gravity	<1.005
	Urea nitrogen	19 mg/dL	U-protein	(2+)
	Creatinine	1.98 mg/dL	U-glucose	(1+)
	Uric acid	4.2 mg/dL	U-blood	(1+)
	Aspartate amino transferase	14 IU/L	U-white blood cell	(−)
	Alanine transaminase	36 IU/L		
	Lactate dehydrogenase	165 IU/L	Urinary sediments	
	Alkaline phosphatase	298 IU/L	Red blood cell	<1/HPF
	Creatine kinase	67 IU/L	White blood cell	1–4/HPF
	Sodium	142 mEq/L	Cast	(−)
	Potassium	4.2 mEq/L	Crystal	(−)
	Chloride	109 mEq/L		
	Calcium	8.8 mg/dL	Urine chemistries	
	Inorganic phosphorus	2.3 mg/dL	U-creatinine	21.5 mg/dL
	C-reactive protein	0.02 mg/dL	U-total protein	46 mg/dL
	Glucose	97 mg/dL	U-albumin	105 mg/dL
	Intact PTH	166.5 pg/mL	U-NAG	10.4 IU/L
			U-β2MG	21366 μg/L
			U-α1MG	86.1 mg/L
			U-glucose	71 mg/L
			U-sodium	36 mEq/L
			U-calcium	36 mEq/L
			U-phosphorus	11.8 mg/dL
			U-potassium	13.3 mEq/L
			FENa	2.3 %
			FECa	3.9 %
			%TRP	52.8 %
			TTKG	3.5
			U-osmotic pressure	258 mOsm/kgH
			S-osmotic pressure	287 mOsm/kgH
</				

Despite the presence of hyperparathyroidism and kidney dysfunction, the fractional excretion of calcium was found to be relatively high, thus, suggesting masked hypercalciuria. With the exception of kidney dysfunction and abnormal urinalysis findings, there were no findings suggesting any other organ abnormalities. Renal ultrasonography and abdominal computed tomography (CT) revealed renal cystic lesions and severe medullary calcification (Fig. 3). The patient underwent renal protective therapy using a renin-angiotensin system inhibitor. However, his kidney dysfunction worsened during the 2 years following his presentation (Fig. 4). His hemoglobin level was preserved at the age of 32 years; however, it gradually decreased from 14.1 to 11.5 g/dL, along with the low excretion of erythropoietin, at the age of 34 years, which may have been the manifestation of renal anemia.

Fig. 2 Urine protein electrophoresis. Urine proteins at the age of 34 years were electrophoresed. Various protein fractions were detected

Fig. 3 Abdominal computed tomography (CT) image indicating renal cysts and severe medullary nephrocalcinosis

Fig. 4 Clinical course of the patient. Kidney function was evaluated as 1/creatinine level (red line). The patient exhibited gradual deterioration of kidney function and progressed to chronic kidney disease (CKD) stage 4 at the age of 34 years

The patient's family tree is shown in Fig. 5. His 5-year-old nephew was also found to have proteinuria since the age of 7 months. The nephew was born to healthy parents via a normal spontaneous vaginal delivery. The nephew's immunological and serological profiles were normal, but the urinary β_2 -microglobulin level was markedly elevated at 74583 $\mu\text{g/L}$. The nephew's pediatrician suspected Dent disease and had closely followed him in the pediatric department. The urinary β_2 -microglobulin level of the nephew's mother—who was the patient's sister—was normal.

Genetic analysis

To investigate a possible genetic mutation in this patient and his nephew, we conducted a genetic analysis. This study complied with the Helsinki Declaration as revised in

Fig. 5 Family tree of the patient. The patient's 5-year-old nephew exhibited elevated low-molecular-weight proteinuria (LMWP) levels, and was suspected of having Japanese Dent (J-Dent). The patient's sister—who is the mother of his nephew—was suspected to be a carrier of J-Dent

2004, and it was approved by the Ethics Committee for Analysis of the Human Genome of the University of Tokyo (Approval No. 3042). Informed consent for genetic analyses was obtained from the patient and the nephew's parents after the nature of the testing, purpose, methods, and potential risks were thoroughly explained. Given the patient's gender, markedly increased LMWP levels, and the absence of signs of any other disease accounting for proximal tubular dysfunction, Dent disease was primarily considered. Genomic DNA was extracted from peripheral blood of the patient, his nephew, and their family members. Assays were performed using QuickGene DNA whole blood kit S (Fujifilm, Japan). Leukocyte DNA was extracted, and all the exons and exon–intron boundaries were amplified using *CLCN5*-specific primers via polymerase chain reaction (PCR) amplification, according to previously described methods [5]. The DNA sequence of the PCR products was determined by *Taq* polymerase cycle sequencing and a semi-automated detection system (ABI 3130xl Genetic Analyzer; Applied Biosystems, Japan). The *CLCN5* gene analysis results of the patient and his nephew revealed a nonsense mutation (Asp130Gly) in exon 4 (Fig. 6). The patient's sister—who was the mother of the patient's nephew—was heterozygous for this mutation.

Discussion

Patients with Dent disease usually develop end-stage renal disease by the fifth decade of life [6]. However, disease activity in most patients with J-Dent is relatively mild compared to that in the other types of Dent disease, such as Dent disease in the UK, XRN in North America, and

Fig. 6 *CLCN5* gene analysis. Gene analysis demonstrated that the patient and his nephew have a nonsense mutation (Asp130Gly) in exon 4. The patient's sister—who is the mother of the patient's nephew—was heterozygous for this mutation

XLHR in Europe. Furthermore, renal function in J-Dent is well preserved, resulting in a low incidence of end-stage renal disease [3, 4]. Murakami and Kawakami [7] reported that, in 52 patients with J-Dent, only 3 had increased serum creatinine levels of more than 1.0 mg/dL and none had end-stage renal disease. However, the majority of patients in this report were pediatric patients, and the prognosis of J-Dent was not thoroughly evaluated. In Japan, the diagnosis of Dent disease is typically made in early childhood by a population-based urine screening program, and the long-term follow-up of these patients is still incomplete. Recently, a few cases of adult J-Dent with advanced kidney dysfunction have been reported [8, 9], suggesting that patients with J-Dent are at risk of developing end-stage kidney failure, similar to the other types of Dent disease.

Our case is significant in that the diagnosis of Dent disease was not made until the patient had reached adulthood. There are several possible explanations for this delay in diagnosis. First, the histological findings of kidney biopsies in patients with Dent disease are nonspecific, ranging from normal to FSGS-like lesions [10, 11]. Murakami and Kawakami [7] reported that the kidney biopsies of patients with J-Dent revealed various abnormal glomerular findings in 34 % (11/32 cases). They found that the glomerular lesions had focal global sclerosis (7/32 cases), mesangial proliferation without hyalinosis (3/32 cases), mesangial proliferation with hyalinosis (1/32 cases), and minor glomerular abnormalities (21/32 cases). Immunofluorescence microscopy analysis further demonstrated that some cases may be accompanied by glomerular immune complex deposition (4/26 cases). They also reported that 23 of 32 cases exhibited normal tubular findings, whereas 9 cases showed tubular atrophy and tubular cast formation. These studies suggest that kidney biopsy findings are not always useful for the diagnosis of Dent disease. However, the detection of characteristic urine abnormalities followed by nephrocalcinosis is essential. As in our case, most of the patients develop Dent disease due

to mutations of the chloride channel gene *CLCN5*, which encodes the chloride transporter expressed on endosomes in the proximal tubules [12]. The functional abnormality of this chloride transporter causes insufficient acidification of endosomes, resulting in impaired endocytosis and failure of the reabsorption of glomerulus-filtered proteins, the primary component of which is LMWP [13, 14]. Furthermore, insufficient endocytosis activity leads to several proximal tubular dysfunctions, resulting in hypercalciuria, hyperphosphaturia, aminoaciduria, glycosuria, and nephrocalcinosis [13, 14]. Thus, when the patients are male and found to have chronic kidney disease (CKD) of unknown etiology along with these proximal tubular dysfunctions, Dent disease should be considered.

Second, Dent disease continues to be a relatively new disease concept. Its clinical characteristics were first described in 1964 by Dent and Friedman [15], and Wrong et al. [16] named it “Dent disease” in 1994. In 1995, the genetic association of this condition with *CLCN5* was identified [17]. In Japan, LMWP with hypercalciuria and nephrocalcinosis was first reported in 1980 [18], and *CLCN5* mutations were found in these patients in 1997 [19]. The concept of Dent disease gradually spread among pediatricians in the new millennium. In contrast, adult nephrologists tend to be less familiar with Dent disease, since they scarcely encounter such patients clinically. As noted in our case, undiagnosed Dent disease may account for some cases of idiopathic kidney failure in young adults. These possible Dent disease cases should be investigated, as their natural histories may help clarify the clinical characteristics and prognosis of J-Dent.

Third, the transition of medical care from childhood to adulthood was not smooth in our case. Many physicians have stressed the importance of a smooth transition, but this continues to be problematic for many young patients. In particular, it is recommended that adolescent patients with CKD stages 3 or 4 should be gradually transferred to an adult clinic with pediatricians and nephrologists

working in close collaboration [20]. In our case, the degree of kidney dysfunction until adolescence was considered to be relatively mild (CKD stage 1 or 2), and, thus, it is possible that patient education highlighting the need for continuous follow-up was insufficient. Adequate ongoing care from pediatricians to nephrologists is extremely important for managing young adults with CKD, even if patients are asymptomatic and have mild kidney dysfunction. Close collaboration between pediatricians and nephrologists will likely contribute to a good prognosis for young adults with CKD.

Currently, there are no specific interventions that will change the natural course and inevitable development of kidney failure in patients with Dent disease. However, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may delay the progression to end-stage kidney failure [10]. Furthermore, kidney transplantation has been found to be effective for Dent disease patients with end-stage kidney failure, and there are no reports of relapse among these patients. To further our knowledge of the natural history of Dent disease and effective interventions, investigations of undiagnosed cases and evaluation of the accurate diagnosis of Dent disease are required. Long-term observational studies will also help us to accurately predict the prognosis.

In conclusion, our case report indicates that J-Dent can cause advanced kidney dysfunction similar to the other types of Dent disease. Thus, when male patients have CKD of unknown etiology along with elevated LMWP levels as well as hypercalciuria, hyperphosphaturia, aminoaciduria, glycosuria, and nephrocalcinosis, Dent disease should be considered. Since many patients with Dent disease develop kidney dysfunction in adulthood, close collaboration between pediatricians and nephrologists is essential. Investigations of undiagnosed adult J-Dent and future research regarding the clinical course of J-Dent will enhance our understanding of its clinical characteristics, prognosis, and effective treatment options.

Acknowledgments We would like to thank Prof. Hidekazu Shigematsu (Department of Pathology, Shinshu University School of Medicine, Japan) for his invaluable assistance with the pathologic analysis.

Conflict of interest The authors have declared that no conflict of interest exists.

References

- Kelleher CL, Buckalew VM, Frederickson ED, Rhodes DJ, Conner DA, Seidman JG, et al. CLCN5 mutation Ser244Leu is associated with X-linked renal failure without X-linked recessive hypophosphatemic rickets. *Kidney Int.* 1998;53:31–7.
- Scheinman SJ. X-linked hypercalciuric nephrolithiasis: clinical syndromes and chloride channel mutations. *Kidney Int.* 1998; 53:3–17.
- Igarashi T, Hayakawa H, Shiraga H, Kawato H, Yan K, Kawaguchi H, et al. Hypercalciuria and nephrocalcinosis in patients with idiopathic low-molecular-weight proteinuria in Japan: is the disease identical to Dent's disease in United Kingdom? *Nephron.* 1995;69:242–7.
- Takemura T, Hino S, Ikeda M, Okada M, Igarashi T, Inatomi J, et al. Identification of two novel mutations in the CLCN5 gene in Japanese patients with familial idiopathic low molecular weight proteinuria (Japanese Dent's disease). *Am J Kidney Dis.* 2001;37:138–43.
- Lloyd SE, Pearce SH, Günther W, Kawaguchi H, Igarashi T, Jentsch TJ, et al. Idiopathic low molecular weight proteinuria associated with hypercalciuric nephrocalcinosis in Japanese children is due to mutations of the renal chloride channel (CLCN5). *J Clin Invest.* 1997;99:967–74.
- Igarashi T. Dent disease: hereditary Fanconi Syndrome: Fanconi Syndrome. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, editors. *Pediatric nephrology*. 6th ed. Berlin: Springer; 2009. p. 1044–478.
- Murakami T, Kawakami H. The clinical significance of asymptomatic low molecular weight proteinuria detected on routine screening of children in Japan: a survey of 53 patients. *Clin Nephrol.* 1990;33:12–9.
- Igarashi T, Inatomi J, Ohara T, Kuwahara T, Shimadzu M, Thakker RV. Clinical and genetic studies of CLCN5 mutations in Japanese families with Dent's disease. *Kidney Int.* 2000;58: 520–7.
- Yanagida H, Ikeoka M, Kuwajima H, Wada N, Tabata N, Sugimoto K, et al. A boy with Japanese Dent's disease exhibiting abnormal calcium metabolism and osseous disorder of the spine: defective megalin expression at the brush border of renal proximal tubules. *Clin Nephrol.* 2004;62:306–12.
- Copelovitch L, Nash MA, Kaplan BS. Hypothesis: Dent disease is an underrecognized cause of focal glomerulosclerosis. *Clin J Am Soc Nephrol.* 2007;2:914–8.
- 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;24:2369–73.
- Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, et al. A common molecular basis for three inherited kidney stone diseases. *Nature.* 1996;379:445–9.
- Piwon N, Günther W, Schwake M, Bösl MR, Jentsch TJ. ClC-5 Cl[−]-channel disruption impairs endocytosis in a mouse model for Dent's disease. *Nature.* 2000;408:369–73.
- Wang SS, Devuyt O, Courtoy PJ, Wang XT, Wang H, Wang Y, et al. Mice lacking renal chloride channel, CLC-5, are a model for Dent's disease, a nephrolithiasis disorder associated with defective receptor-mediated endocytosis. *Hum Mol Genet.* 2000;9: 2937–45.
- Dent CE, Friedman M. Hypercalciuric rickets associated with renal tubular damage. *Arch Dis Child.* 1964;39:240–9.
- Wrong OM, Norden AGW, Feest TG. 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. *QJM.* 1994;87:473–93.
- Fisher SE, van Bakel I, Lloyd SE, Pearce SH, Thakker RV, Craig IW. Cloning and characterization of CLCN5, the human kidney chloride channel gene implicated in Dent disease (an X-linked hereditary nephrolithiasis). *Genomics.* 1995;29:598–606.

18. Suzuki Y, Okada T, Higuchi A, Mase D, Kobayashi O. Asymptomatic low molecular weight proteinuria: a report on 5 cases. *Clin Nephrol.* 1985;23:249–54.
19. Akuta N, Lloyd SE, Igarashi T, Shiraga H, Matsuyama T, Yokoro S, et al. Mutations of CLCN5 in Japanese children with idiopathic low molecular weight proteinuria, hypercalciuria and nephrocalcinosis. *Kidney Int.* 1997;52:911–6.
20. Watson AR, Harden P, Ferris M, Kerr PG, Mahan J, Ramzy MF. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Pediatr Nephrol.* 2011;26:1753–7.