Hypothesis: Dent Disease Is an Underrecognized Cause of Focal Glomerulosclerosis

Lawrence Copelovitch,* Martin A. Nash,† and Bernard S. Kaplan*
*Department of Pediatrics, Division of Nephrology, The Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania; and †Department of Pediatrics, Division of Nephrology, Columbia University Medical Center, New York, New York

Background and Objectives: Dent disease is a hereditary form of progressive renal failure characterized by hypercalciuria and proximal tubular dysfunction. The clinical presentation is often insidious with the majority of patients remaining asymptomatic throughout childhood. Despite the seemingly mild, early course, more than 20% of 32 asymptomatic patients in one study had biopsy evidence of focal glomerulosclerosis. Furthermore, end-stage renal disease often occurs in men in early to middle adulthood.

Design, Setting, Participants, & Measurements: This article describes two male patients who presented with asymptomatic proteinuria and were found to have focal glomerulosclerosis. Despite the absence of nephrocalcinosis on renal ultrasound, the diagnosis of Dent disease was considered because of unexplained proteinuria. Subsequent history revealed renal calculi in each maternal family.

Results: The clinical diagnosis of Dent disease was established by intermittent hypercalciuria and low molecular weight proteinuria and confirmed through mutational analysis.

Conclusions: It is hypothesized that a diagnosis of Dent disease may be unrecognized in patients with unexplained proteinuria and idiopathic focal glomerulosclerosis.


Focal segmental glomerulosclerosis (FSGS) is an important cause of proteinuria and nephrotic syndrome in pediatric patients and is now the most frequent cause of nephrotic syndrome in adults (1). There is also substantial risk for progression to ESRD. The histopathologic findings in FSGS can be secondary to systemic conditions that include chronic hypoxemia, reduced nephron mass, HIV infection, and obesity. Similar histopathologic findings are seen in idiopathic (primary) FSGS. These nonspecific histopathologic findings are the reaction of the glomerulus to many types of injury and do not represent a single disease.

In the past 10 yr, studies on the podocyte and its related proteins have added to our understanding of the inherited forms of idiopathic FSGS. Mutations in the Podocin gene, α-Antitinin 4 gene, and CD2AP gene cause inherited FSGS (1). These proteins are located in the podocyte foot process and have a critical role in podocyte function, structure, and interactions with the extracellular lipid rafts. Despite these significant advances, the cause of the majority of cases of FSGS remains unknown.

Primary FSGS may also result from undefined circulating factors or cytokines that alter the permeability of the glomerular barrier. Observations that support the hypothesis that there is a circulating factor include the response of some cases of FSGS to medications that suppress lymphocyte function, the recurrence of nephrotic syndrome after renal transplantation, and the injection of serum from patients with FSGS into healthy rats with a resultant nephrotic syndrome (2). Despite numerous attempts, the isolation of these factors has remained elusive.

In addition to the podocyte-related and immunologic-mediated causes of focal sclerosis, several tubulopathies (Dent disease, Gitelman syndrome, Bartter syndrome, and inherited distal renal tubular acidosis) have been associated with focal glomerulosclerosis (3–9). This further suggests that the entity known as focal glomerulosclerosis is not a singular diagnosis but rather a final common pathway resulting from injury that occurs at multiple areas of the nephron. Although systemic conditions, reduced nephron mass, inherited podocytopathies, and immune dysregulation all have been well established as causes of focal sclerosis, we wish to add the primary tubulopathies to the growing list of causes.

In this case report, we review the literature and report two children who had Dent disease and developed significant proteinuria and biopsy-proven focal glomerulosclerosis. We believe that primary tubulopathies, in particular Dent disease, should not be overlooked in the differential diagnosis when considering a patient with idiopathic focal glomerulosclerosis.

Case Reports

Patient 1
A 12-yr-old boy was referred for evaluation of asymptomatic proteinuria detected on a routine sports physical examination.
During the preceding two years, he was noted to have orthostatic proteinuria with negative tests on first-morning specimens. The proteinuria was subsequently also present in first-morning samples. The patient did not have edema, gross hematuria, or recent illnesses. Pregnancy and birth were normal and term; however, ABO incompatibility required blood transfusions.

**Family History.** A maternal grandfather had a history of renal calculi; he died at 67 yr from glomerulosclerosis, hypertension, and end-stage renal failure that required dialysis. The patient’s father received a diagnosis of nerve deafness at 9 yr and wears hearing aids. His mother was diagnosed with a bifurcated uterus and an incompetent cervix.

**Physical Examination.** The boy’s height was 138.3 cm (fifth to 10th percentile), his weight was 35 kg (10th to 25th percentile), and his BP was 90/50 mmHg. There were no dysmorphic features. He had normal nails and patellae, normal cardiac examination, no rashes, no arthritis, and no periorbital or pedal edema.

**Laboratory Studies.** Initial serum concentrations all were normal: Sodium 137 mEq/L, potassium 3.8 mEq/L, chloride 102 mEq/L, carbon dioxide 25 mEq/L, calcium 9.5 mg/dl, phosphorous 3.8 mg/dl, albumin 4.7 g/dl, total cholesterol 201 mg/dl, creatinine 1.0 mg/dl, C3 107 mg/dl, and C4 38 mg/dl. Initial urine protein/creatinine ratio was 1.6 mg/mg. Twenty-four-hour protein excretion was 1283 mg/24 h. Creatinine clearance as estimated by the Schwartz formula was 79 ml/min per 1.73 m². During the subsequent 5 mo, the 24-h protein clearance estimated by the Schwartz formula was 95 ml/min.

**Imaging Studies.** A renal ultrasound showed normal-sized kidneys for age and height. The right measured 7.3 cm, and the left measured 8.0 cm. There was normal echotexture and no evidence of a calculus or nephrocalcinosis.

**Renal Biopsy.** Thirty-seven glomeruli were present for light microscopy analysis. There were areas of focal global glomerulosclerosis (FGGS). Twenty-five percent (nine of 37) of the glomeruli were globally sclerotic. There was slight tubular atrophy and interstitial fibrosis involving <5% of the cortex. Direct immunofluorescent microscopy of the nonsclerotic glomeruli was minimally positive for IgM in the mesangium of several glomeruli. Staining for IgG, IgA, C3, and C1q was negative. Electron microscopy revealed no electron-dense deposits and a normal glomerular basement membrane. The visceral epithelial cells had effacement of 10% of the foot processes.

**Course.** Two months after treatment with enalapril, there was moderate reduction in protein excretion to 880 mg/24 h. The family obtained a second opinion, and a diagnosis of Dent disease was considered. The initial spot urine calcium/creatinine ratio was 0.8 (normal <0.2), and the β2-microglobulin excretion was 32,203 μg/L (normal 1 to 160 μg/L). During the past year, the urinary calcium excretion has only been intermittently elevated.

Analysis of the CLCN5 gene showed a duplication of the “A” nucleotide at the 523rd base of the sixth exon (523dupA). The resulting frameshift mutation in the 175th codon (Thr175fsX8) causes a premature stop codon sequence eight residues downstream from the duplication. This analysis was performed by GeneDx (Gaithersburg, MD).

**Patient 2**

A 9-yr-old boy was referred for evaluation of asymptomatic proteinuria. At 1 yr of age, he had intermittent fevers and hepatosplenomegaly. An extensive metabolic and hematologic evaluation for a cause of the hepatosplenomegaly was negative. The fevers resolved, and during the next 8 yr, he remained asymptomatic. However, the slightly enlarged spleen and liver persisted. At the age of 4 yr, he was evaluated for urinary frequency and dysuria. A urine dipstick showed microscopic hematuria and 300 mg/dl protein. Subsequent studies revealed a normal renal ultrasound, normal serum electrolytes, normal serum creatinine, normal serum albumin, 1321 mg of protein in a 24-h urine collection, and persistent proteinuria in a first-morning sample. At the age of 7 yr, his serum creatinine began to increase to 1.0 mg/dl and, a renal biopsy was performed. Five glomeruli were available for analysis; two were globally sclerotic and three were normal. We first saw the patient for a second opinion 2 mo after his initial renal biopsy. At that time, he did not have edema, gross hematuria, or recent illnesses. We elected to repeat a kidney biopsy.

**Family History.** Both maternal grandparents had a history of renal calculi. A maternal aunt had a history of hearing loss. His mother has antiphospholipid antibodies and has had two miscarriages. There is no family history of kidney failure.

**Physical Examination.** The boy’s height was 129.7 cm (25th percentile), his weight was 27.6 kg (50th percentile), and his BP was 95/62 mmHg. There were no dysmorphic features. He had normal nails and patellae; normal cardiac examination; and no rashes, arthritis, or peripheral edema. The abdomen was soft and nontender. The liver was not enlarged, and the spleen was palpable two finger breadths below the costal margin.

**Laboratory Studies.** Initial serum concentrations all were normal: Sodium 141 mEq/L, potassium 3.9 mEq/L, chloride 105 mEq/L, carbon dioxide 25 mEq/L, calcium 9.6 mg/dl, phosphorous 4.4 mg/dl, albumin 4.7 g/dl, and total cholesterol 201 mg/dl. The serum creatinine concentration was 0.9 mg/dl. Creatinine clearance as estimated by the Schwartz formula was 79 ml/min per 1.73 m².

**Imaging Studies.** A renal ultrasound showed normal-sized kidneys for age and height. The right measured 8.0 cm, and the left measured 7.6 cm. There was minimal pelvicviectasis bilaterally, normal echotexture, and no evidence of calculi or nephrocalcinosis.

**Renal Biopsy.** Six glomeruli were evaluated by light microscopy. There were areas of focal global and segmental glo-
merulosclerosis. Two of the glomeruli were globally sclerotic, two to three glomeruli were segmentally sclerosed in some levels and globally scleroses in others, and one glomerulus was completely normal. Periglomerular fibrosis was seen around one glomerulus. There was patchy, mild interstitial chronic inflammation and proteinaceous casts in some tubules. Other tubules contained granular calcifications. The material examined for immunofluorescence did not contain any glomeruli. Electron microscopy revealed no electron-dense deposits and a uniform capillary basement membrane thickness with some wrinkling in the perimesangial region. The visceral epithelial cells had variable effacement of several of the foot processes.

**Course.** The family deferred starting a trial of enalapril. During the past 5 yr, the creatinine has increased to 1.3 mg/dl. Subsequent to the renal biopsy, a diagnosis of Dent disease was considered. The spot urine calcium/creatinine ratio was 0.07 (normal <0.2), the β2-microglobulin excretion was 52,700 μg/L (normal 1 to 160 μg/L), and there was a generalized aminoacidaemia.

Analysis of the CLCN5 gene showed a duplication of 3 bp at the 744th bp in the seventh exon (c744_746dupACG). The resulting insertion of an alanine residue at codon 249 is thought to disrupt a highly conserved series of five alanine residues, thereby disrupting a D5 transmembrane domain. This analysis was performed by GeneDx (Gaithersburg, MD).

**Discussion**

Proximal tubular dysfunction is more common when the nephrotic syndrome is associated with FSGS than with minimal-change nephrotic syndrome (10,11). Furthermore, patients with minimal-change nephrotic syndrome rarely have tubulo-interstitial involvement, whereas those with FSGS often have tubulointerstitial infiltration and fibrosis (12). Most investigators have assumed that the nonselective proteinuria in FSGS causes proximal tubular cell injury with the resultant tubulo-interstitial damage and scarring. Valles et al. (13) evaluated urinary β2-microglobulin and N-acetyl-β-D-glucosaminidase levels (low molecular weight proteins) in 11 patients with FSGS and found no correlation between the degree of interstitial fibrosis and low molecular weight proteinuria. Consistent with these observations, we challenge the universality of the accepted chronology of events that suggests that nonselective proteinuria in focal sclerosis causes tubulointerstitial damage and fibrosis that causes tubular dysfunction. We propose that in some cases of FSGS, the tubular dysfunction or damage is the primary renal insult and that the glomerulosclerosis may be a secondary epiphenomenon.

In several animal models, high-grade nonselective proteinuria results in proximal tubular swelling, toxicity, and eventual tubulointerstitial inflammation (14,15). It is interesting that none of these models has demonstrated that the end result of these tubular insults is wasting of glucose, amino acids, or electrolytes. The inherited tubulopathies provide a clear example of renal diseases in which the initial damage is tubular but the end result is FSGS. For example, there are a few reports of FSGS associated with Dent disease (3–5), Gitelman syndrome (6,7), Bartter syndrome (8), and inherited distal renal tubular acidosis (9). ESRD can occur between the ages of 25 and 50 yr in patients with Dent disease (16). However, data on the long-term outcomes of patients with Gitelman and Bartter syndromes is scanty but important in regard to our hypothesis. Eighteen patients with Bartter syndrome in the North American Pediatric Renal Cooperative Study database had renal failure. Unfortunately, the specific causes of the renal failure were not available (7). ESRD has also been reported in Gitelman syndrome (17,18), but histologic findings were not included in the reports.

Bouissou et al. (19) described nine children with proximal tubular dysfunction noted 2 to 25 mo after diagnosis of steroid-resistant nephrotic syndrome. There were combinations of glucosuria, hypokalemia, metabolic acidosis, hypophosphatemia, and hypouricemia (19). McVicar et al. (20) reported five cases of childhood nephrotic syndrome associated with renal glucosuria and other tubular defects and suggested that these were early manifestations of FSGS. The proximal tubular defects were noted within the first 3 to 22 mo of diagnosis and at a time when the level of renal function was either normal or slightly depressed (GFR 56 to 90 ml/min per 1.73 m²). All of the children had renal glucosuria as the initial tubular defect, and several also developed aminoaciduria, bicarbonaturia, and phosphaturia. Two of the five patients had near-normal renal function at the time of their initial tubular dysfunction and no evidence of FSGS or interstitial pathology in the initial biopsy specimen. These findings could suggest that a proximal tubular defect preceded the onset of the glomerulosclerosis.

Dent disease is an X-linked renal tubular disorder that is characterized by low molecular weight proteinuria, hypercalciuria, nephrolithiasis, and progressive renal failure. Glucosuria, aminoaciduria, metabolic acidosis, and hypophosphatemia can also occur. X-linked recessive nephrolithiasis, X-linked recessive hypophosphatemic rickets, and the idiopathic low molecular weight proteinuria of Japanese children all are caused by the mutations in the same voltage-gated chloride channel CLCN5 that result in the Dent disease. They are now collectively referred to as Dent disease on the basis of phenotypic similarities and common genetic cause (21). In a study of 32 children who underwent renal biopsy, Murakami et al. (4) found that 22% of asymptomatic Japanese children with idiopathic low molecular weight proteinuria had FGGS. On the basis of the relatively high percentage of patients who had Dent disease and developed focal glomerulosclerosis in the report of Murakami et al. (4) and the frequency of early proximal tubular dysfunction in two case series (19,20), we suggest that Dent disease may not be recognized when it presents as idiopathic focal glomerulosclerosis and perhaps steroid-resistant nephrotic syndrome. This could result in unnecessary treatment with high dosages of corticosteroids and immunosuppressive agents.

Focal sclerotic lesions of glomeruli can be differentiated into two types: FSGS, involving only part of the glomerular tuft, and FGGS, with complete obsolescence in a variable number of glomeruli. FGGS can be seen as part of the normal involution of nephrons. The number of such glomeruli is <10% in 95% of the population under 40 yr of age (22,23). In infants, the presence of
an occasional global sclerotic glomerulus may represent an error in nephron formation. In pathologic conditions, such as idiopathic nephrotic syndrome, both focal segmental and global lesions may be seen as part of the progression of focal sclerosis to sclerosis of the entire glomerulus, particularly when associated with tubular atrophy. It has been suggested that children with the nephrotic syndrome and only FGGS without tubular atrophy form a subgroup with a more favorable prognosis, not unlike that of children with minimal-change disease (22,23).

Patients with Dent disease and glomerular abnormalities on renal biopsy usually have FGGS. The tubulointerstitial findings are variable and range from normal to interstitial fibrosis or tubular atrophy (3,4). Because of the irregularity of the sclerotic process, the presence of one or more segmentally sclerotic lesions can occur. Whether FGGS is invariably a separate entity from FSGS or is part of a continuum has yet to be fully determined. Frymoyer et al. (16) described at least one patient who had Dent disease and had renal biopsy findings that showed that 25% of the glomeruli had "partial-to-global sclerosis." One helpful diagnostic point is that the electron microscopy findings in Dent disease show minimal effacement of the epithelial foot processes, in contrast to FSGS with nephrotic syndrome.

We believe that given the lack of convincing evidence in the literature, the diagnosis of Dent disease should be considered in patients with both FGGS and FSGS.

Focal glomerulosclerosis is a nonspecific histologic finding that seems to be the reaction of the glomerulus to a variety of renal insults. Various tubulopathies have been associated with focal glomerulosclerosis. Dent disease is potentially the most important of these causes because it often goes unrecognized as a result of the mild initial clinical features, the absence of overt serum electrolyte abnormalities, and the low incidence (5 to 10%) of glucosuria on routine urinalysis (4). Furthermore, as was noted in our patients, even when the diagnosis is considered, hypercalciuria may not be a constant finding. For reasons that are still unclear, Dent disease may result in ESRD between the ages of 25 and 50 yr. We recommend early consideration of the diagnosis of Dent disease in all cases of unexplained proteinuria and idiopathic focal sclerosis. This can be done initially by screening the urine for excretion of calcium and β2-microglobulin. An accurate diagnosis could prevent needless exposure to potentially hazardous cytotoxic medications in some patients. Furthermore, Cebotaru et al. (24) fed high-citrate diets to CIC-5 knockout mice (a murine model of Dent disease) and significantly delayed progression of renal disease. If these findings translate to human patients, then making the appropriate diagnosis could be important.

Disclosures
None.

References

