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Recommended Citation

Solano, A., Lew, S.Q., Ing, T.S. (2014). Dent–Wrong disease and other rare causes of the Fanconi syndrome. *Clinical Kidney Journal*, 7(4), 344-347.

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Minireview

Dent–Wrong disease and other rare causes of the Fanconi syndrome

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Abstract

Dent–Wrong disease, an X-linked recessive disorder of the proximal tubules, presents with hypercalciuria, nephrocalcinosis, nephrolithiasis, renal insufficiency, low-molecular-weight proteinuria, rickets and/or osteomalacia. Dent and Friedman initially characterized the disorder in 1964 following studies of two patients with rickets who presented with hypercalciuria, hyperphosphaturia, proteinuria and aminoaciduria. Since then, extensive investigation identified two genetic mutations (CLCN5 and OCRL1) to be associated with Dent–Wrong disease. Clinical features supported by laboratory findings consistent with proximal tubule dysfunction help diagnose Dent–Wrong disease. Genetic analysis supports the diagnosis; however, these two genes can be normal in a small subset of patients. The differential diagnosis includes other forms of the Fanconi syndrome, which can be hereditary or acquired (e.g. those related to exposure to exogenous substances). Treatment is supportive with special attention to the prevention of nephrolithiasis and treatment of hypercalciuria. We review the rare forms of Fanconi syndrome with special attention to Dent–Wrong disease.

Keywords: Dent–Wrong disease; Dent's disease; Fanconi syndrome; hypercalciuria; hyperphosphaturia

Introduction

Fanconi syndrome represents a generalized dysfunction of the proximal tubule with varying degrees of wasting of any substance normally reclaimed by proximal tubule cells [1]. Phosphate, glucose, amino acid and bicarbonate wasting produce clinical consequences. Children present with rickets and impaired growth. Adults present with bone diseases such as osteomalacia and osteoporosis. The clinical constellation of symptoms includes metabolic acidosis, hypokalemia, hypouricemia, hypophosphatemia, glycosuria, polyuria, sodium wasting, hypercalciuria and low-molecular-weight (LMW) proteinuria or aminoaciduria [2].

A Swiss pediatrician, Guido Fanconi [3], described a child who had glycosuria and albuminuria in addition to rickets and dwarfism [4]. The syndrome bears his name.

The etiology of Fanconi syndrome is incompletely defined and probably varies with each cause. Variants of Fanconi syndrome may be inherited or acquired (Table 1).

Acquired Fanconi syndrome may occur at any age depending upon the timing of exposure to noxious toxins and drugs that injure the proximal tubule.

Genetic conditions such as Wilson disease, late-onset forms of cystinosis and galactosemia present with Fanconi syndrome later in life as toxic materials accumulate over time resulting in progressive proximal renal tubular damage [1].

Inherited causes of Fanconi syndrome include hereditary fructose intolerance, Lowe syndrome and Dent–Wrong disease [5]. Hereditary fructose intolerance results in a

deficiency of the aldolase B enzyme, which cleaves fructose 1-phosphate. After ingesting fructose, accumulation of fructose 1-phosphate leads to sequestration of inorganic phosphate and deficiency of adenosine triphosphate (ATP). ATP deficiency causes impaired proximal tubular function or Fanconi syndrome. Other associated symptoms include hypoglycemic shock, severe abdominal symptoms and impaired function of the Krebs cycle that produces metabolic acidosis and is exacerbated by impaired renal bicarbonate reabsorption [6].

Characteristic features of Lowe (oculocerebrorenal) syndrome include congenital cataracts, mental retardation, muscular hypotonia and renal Fanconi syndrome [7]. In contrast, Dent–Wrong disease remains confined mainly to the kidney. Both diseases display LMW proteinuria with varying degree of glycosuria, aminoaciduria and phosphaturia. Proximal renal tubular acidosis may be severe in Lowe syndrome causing growth retardation. Rickets is thought to be a consequence of hypophosphatemia in Dent–Wrong disease and acidosis in Lowe syndrome. Hypercalciuria, a characteristic of Dent–Wrong disease, leads to nephrocalcinosis or nephrolithiasis. Renal failure progresses to end-stage renal disease in young adulthood in Dent–Wrong disease and earlier in patients with Lowe syndrome. Dent–Wrong disease will be the focus of this review.

Dent–Wrong disease

Dent and Friedman initially described what has been called Dent's disease in 1964 when they reported two

Table 1. Proximal RTA with Fanconi Syndrome

Genetic	NaPi-II co-transporter mutation
Inherited systemic disease	Cystinosis Tyrosinemia Hereditary fructose intolerance Galactosemia Glycogen storage disease (Type I) Mitochondrial disorders Wilson's disease Lowe syndrome Dent's disease Fanconi–Bickel syndrome
Acquired causes	
Drug-induced	
Nucleotide reverse transcriptase inhibitors	Tenofovir, adefovir
Nucleoside reverse transcriptase inhibitors	Didanosine, lamivudine, stavudine
Anticancer drugs	Ifosfamide, oxaplatin, cisplatin
Anticonvulsant drugs	Valproic acid
Antibiotics	Aminoglycoside, expired tetracyclines
Antivirals	Cidofovir
Other	Streptozocin
Miscellaneous conditions	
Heavy metals	Lead, cadmium, mercury and copper
Vitamin D deficiency	
Multiple myeloma	
Amyloidosis	
Renal transplantation	
Paroxysmal nocturnal hemoglobinuria	
Aristolochic acid	
Fumaric acid	
Suramin	
Paraquat	
L-lysine and L-arginine	
Tubulo-interstitial nephritis	
Membranous nephropathy with antitubular antibodies	

Permission to reproduce table granted by Oxford University Press [1].

patients with rickets and urinary findings of hypercalciuria, hyperphosphaturia, proteinuria and aminoaciduria [8]. This rare disorder affects ~250 families. Dent–Wrong disease, an X-linked recessive disorder of the proximal tubules, presents with clinical features of Fanconi syndrome, LMW proteinuria, hypercalciuria with calcium nephrolithiasis, nephrocalcinosis, hyperphosphaturia, hypophosphatemic rickets and progressive renal failure [2, 9]. Some of the affected individuals have mutations that inactivate a voltage-gated chloride transporter CLC-5.

The CLC-5 transporter-affected individuals have mutations in the CLCN5 gene located on chromosome Xp11.22 encoding a lysosomal transport protein, CLC-5, a voltage-gated chloride transporter [9, 10]. CLC-5 belongs to the CLC family of chloride transporters [5, 10, 11]. CLCN5 gene encodes the CLC-5 chloride channel, a 746-amino acid protein [12]. Defects in CLCN5 define Dent–Wrong disease 1.

CLC-5 co-localizes with the proton-ATPase in subapical endosomes of the proximal tubule cells. These endosomes process proteins that the glomeruli filter and are subsequently taken up by the proximal tubule through adsorptive endocytosis. Proton-ATPase acidifies the endosomal space, releasing the proteins from membrane-binding sites and making them available for proteolytic degradation. CLC-5 mediates electrogenic exchange of chloride for protons in these endosomes, dissipates the positive charge generated by proton entry and may provide a brake or set point for endosomal acidifications. Mutations that inactivate CLC-5 interfere with the mechanism for reabsorption of LMW proteins, thus bringing about LMW

proteinuria. Glycosuria, aminoaciduria and phosphaturia are less consistently seen.

Mutations in the OCRL1 gene which defines Lowe syndrome can also induce a Dent–Wrong-like phenotype, Type 2 Dent–Wrong disease [7, 13]. This gene has a locus on the X chromosome, Xq25 and encodes a phosphatidylinositol 4,5-bisphosphate 5-phosphatase. This phosphatase sits on the trans-Golgi network in renal epithelial cells where it directs protein to the appropriate membrane. Of the 32 families with the clinical diagnosis of Dent–Wrong disease, 19 had mutations in CLCN5 and 5 had mutations in OCRL1, but the diagnosis of Lowe syndrome had been excluded in the members of the latter families because cataracts were absent [14]. A subset of patients with Dent–Wrong disease do not have any mutations in either of the above genes [14].

The CLC-5 protein and the OCRL1 phosphatase interact with the actin cytoskeleton and participate in endosomal apparatus assembly. Similarities in renal features of these two syndromes may be the result of defective membrane trafficking.

CLC-5 presents in the membrane of pre-endocytic vesicles below the brush border of the proximal tubule [12]. It facilitates the entry of Cl⁻ that partakes in active acidification of the vesicles by a proton pump. Lack of this Cl⁻ channel interferes with protein reabsorption from the tubule through the megalin–cubilin receptor system [2]. Such a lack also leads to a disturbance of cell surface receptor recycling via the sodium/proton exchanger NHE3, and the sodium/phosphate transporter NPT2a. The above abnormalities may explain phosphaturia, glycosuria and aminoaciduria [15].

Clinical manifestations

Manifestations usually occur during childhood and those affected present with bone pain and difficulty in walking due to rickets, or symptoms of renal stones such as abdominal pain and hematuria [2, 16]. Occasionally, patients seek additional consultation as a result of the fortuitous discovery of proximal tubular dysfunction, including LMW proteinuria [17]. Symptomatic disease occurs almost exclusively in males, with inheritance being X-linked recessive [16].

Renal manifestations of Lowe (oculocerebrorenal) syndrome include those of Dent–Wrong disease. However, patients with Lowe syndrome also have renal tubular acidosis, congenital cataracts and mental retardation, findings which are absent in Dent–Wrong disease [7].

Diagnosis

The clinical diagnosis of Dent–Wrong disease requires the presence of all three of the following criteria: (i) LMW proteinuria (elevation of urinary excretion of β_2 -microglobulin, Clara cell protein and/or retinol-binding protein by at least 5-fold above the upper limit of normal), (ii) hypercalciuria (>4 mg/kg of body weight in a 24 h urine collection) and (iii) at least one of the following: nephrocalcinosis, calcium nephrolithiasis, hematuria, hypophosphatemia or chronic kidney disease [16, 17]. The excretion of LMW proteins in the urine such as albumin, β_2 -microglobulin and α_1 -microglobulin continues to be the most reliable feature of the disease. The degree of proteinuria remains relatively constant, between 0.5 and 2 g/day in adults and up to

1 g/day in children [2, 16, 18]. Albumin excretion represents less than half of the proteins excreted. LMW proteinuria does not produce any systemic symptoms whereas hypercalciuria can cause nephrolithiasis or nephrocalcinosis.

Hypercalciuria appears in most cases of Dent–Wrong disease and begins in childhood. Nephrolithiasis occurs in ~50% of male patients. Stone constituents include calcium phosphate or a mixture of calcium phosphate and calcium oxalate [2]. Nephrolithiasis presents during the teenage years. Radiological nephrocalcinosis of the medullary type affects male patients and occasionally female patients. Serum levels of 1,25-vitamin D and 25-vitamin D remain normal.

Aminoaciduria, glycosuria, acidosis, hypokalemia and progressive renal failure present inconsistently. End-stage renal disease commonly arises in the fifth decade (47 ± 13 years). Renal biopsy specimens show chronic interstitial nephritis with scattered calcium deposits [2, 16]. Prominent tubular atrophy with diffuse inflammatory infiltrate composed of lymphocytes, and foci of calcification around and within epithelial cells can be seen. Glomeruli generally have normal architecture but may have hyalinization. However, a rare case of biopsy-proven focal glomerulosclerosis was described [19].

The identification of a mutation in either *CLCN5* or *OCRL1* confirms the diagnosis. However, a minority of patients will not have either mutation present [7]. Among those with supportive clinical findings, a negative genetic test does not rule out this disease.

The absence of clinical cataracts and the lack of severe intellectual deficit are key features that make a diagnosis of Dent–Wrong disease 2, associated with *OCRL1* mutations, more likely than a diagnosis of Lowe syndrome.

Males who have homozygote genes in this X-linked disease suffer more severely. Females have mild symptoms but become carriers. Females transmit the disease to half of their sons and half of their daughters will be carriers. All the daughters of affected males will be carriers as they will have inherited the X chromosome harboring the mutation. All the sons of affected fathers who have inherited the Y chromosome and not the X chromosome, will be normal.

Treatment

Dent–Wrong disease does not have a specific treatment. Supportive therapy alleviates symptoms and prevents nephrolithiasis. The main focus centers on calcium metabolism to prevent bone disease, kidney stone formation and nephrocalcinosis. Calcium nephrolithiasis management includes increasing fluid intake. Dietary calcium restriction to reduce calcium excretion may contribute to bone disease and, therefore, should be avoided [10]. Low-dose thiazide diuretics may decrease calciuria [20, 21]. However, since these patients waste sodium, they respond with excessive diuresis, kaliuresis and low blood pressure [2, 20]. Rickets in children can be cured by the administration of pharmacological doses of vitamin D. Osteomalacia in adults can also be corrected with vitamin D treatment. However, vitamin D supplement to treat rickets should be used with caution since enhanced gastrointestinal absorption of calcium may exacerbate calcium excretion, calcium nephrolithiasis and nephrocalcinosis. Monitoring urine calcium excretion before and after vitamin D therapy would be prudent [10].

As with any renal disease, acceleration to renal failure can be prevented by avoiding nephrotoxic agents, extreme

high or low blood pressures and postrenal obstruction. A future intervention may include high-dose oral citrate, which delayed renal failure progression in a *CLC-5* knockout mouse model even in the absence of stone formation [22].

Conclusion

Dent–Wrong disease, a rare form of proximal tubular dysfunction, represents a genetically X-linked recessive inherited disorder with male predominance. Symptoms of polyuria, microscopic hematuria, asymptomatic proteinuria or kidney stones presenting in childhood lead to diagnosis. Mutations in the *CLCN5* gene located on chromosome Xp11.22 occur in 60% of affected patients (Dent–Wrong disease 1) and *OCRL1* gene located on chromosome xq25 in 15% of patients (Dent–Wrong disease 2).

CLCN5 mutations inactivate a voltage-gated chloride transporter that exists almost exclusively in the kidney proximal tubule cells. It functions to acidify the endosomes through an ATPase pump to allow exchange of a chloride for a proton. Inactivation of the *CLC-5* leads to generalized dysfunction of the proximal tubule. *OCRL1* encodes a phosphatidylinositol bisphosphate 5-phosphatase, which also affects endosomal trafficking. Lowe (oculocerebrorenal) syndrome, also characterized by proximal tubular dysfunction, has mutations in the *OCRL1* gene too; however, there is genetic heterogeneity in the type of mutations. This may explain the phenotypic differences from Dent–Wrong disease by the presence of congenital cataracts, mental retardation and tubular acidosis. The diagnosis for Dent–Wrong disease can be made clinically by the presence of LMW proteinuria, hypercalciuria and at least by one of the following criteria: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia or chronic kidney disease. End-stage renal failure occurs between the third and fifth decades of life. Demonstrating the mutations affecting *CLCN5* or *OCRL1* gene confirms the diagnosis; however, a minority of patients will have no identifiable mutation suggesting involvement of other genes. Treatment includes symptomatic relief and prevention of nephrolithiasis by (i) increasing fluid intake, (ii) using thiazide diuretics to reduce calcium excretion and (iii) careful supplementing vitamin D. Dietary calcium reduction should be avoided.

Authors' note

The term, Dent's disease, was coined by Professor Charles Dent's very good friend and mentee, Professor Oliver M. Wrong. The latter, along with Professors AGW Norden, TG Feest, SJ Scheinman, RV Thakker and others collaborated to elucidate the disease in large measure. 'We should actually call it Dent–Wrong disease' [23], says Professor Raj Thakker of Oxford's Nuffield Department of Clinical Medicine. After all, he points out, 'Wrong invested even more in its investigation than Dent himself [23]'. Many other authors fully embraced this recommendation [24–26].

Acknowledgement.

Conflict of interest statement. The authors of this manuscript do not have any conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Received for publication: 1.6.14; Accepted in revised form: 10.6.14