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Case Report / Olgu Sunumu

A case of Type 1 Dent disease presenting with isolated persistent proteinuria

İzole persistan proteinüri ile başvuran bir olguda Tip 1 Dent hastalığı

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The known about this topic

Dent disease is characterized by the triad of low molecular-weight proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis. A rare X-linked recessive tubular disorder is caused by *CLCN5* or OCRL gene mutations.

Contribution of the study

The importance of researching low molecular weight proteinuria and considering Dent disease in differential diagnosis has been emphasized in children presenting with isolated persistant proteinuria.

Abstract

Dent disease is a rare X-linked recessive tubular disorder, characterized by the triad of low molecular-weight proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis. It is caused by mutations in the *CLCN5* gene or *OCRL* gene. Thirty to 80% of affected males develop end-stage kidney disease between the ages of 30 and 50 years. Some children were reported to present with isolated persistent proteinuria and a part of these patients were diagnosed as having focal segmental glomerulosclerosis with kidney biopsy. Although there is no specific treatment, treatment of proteinuria and hypercalciuria is thought to delay the progression of the disease. For this reason, awareness of the disease findings and early diagnosis are important. In this case report, we present a boy followed-up with isolated persistent proteinuria and then diagnosed as having Dent disease with mutation analysis that showed c.328_330delT (p.Phe110Trpfs27*) in the *CLCN5* gene. The importance of researching low-molecular- weight proteinuria and considering Dent disease in the differential diagnosis of children presenting with isolated persistent proteinuria has been emphasized.

Keywords: Dent disease, hypercalciuria, isolated persistent proteinuria

Öz

Dent hastalığı, düşük moleküler ağırlıklı proteinüri, hiperkalsiüri, nefrokalsinoz ya/ya da nefrolitiyazis üçlüsü ile belirgin; X'e bağlı çekinik geçiş gösteren nadir bir hastalıktır. Hastalığa *CLCN5* veya *OCRL* genlerindeki mutasyonlar neden olmaktadır. Klasik üçlüsüne rağmen bazı hastaların izole proteinüri ile başvurduğu, bu hastaların bir kısmının böbrek biyopsisi ile fokal segmental glomerulosklerozu tanısı aldıkları bildirilmiştir. Etkilenen erkek hastaların %30-80'inde 3-5. dekadlarda son dönem böbrek hastalığı gelişmektedir. Antiproteinürik tedavi ve hiperkalsiürinin düzeltilmesi ile hastalığın ilerlemesinin yavaşlatılabileceği düşünülmektedir. Bu nedenle hastalığa ait bulguların farkında olmak ve erken tanı önemlidir. Burada, izole persistan proteinüri ile başvuran, düşük moleküler ağırlıklı proteinüri, hiperkalsiüri ve medüller nefrokalsinoz saptanarak Dent hastalığı düşünülen ve *CLCN5* genindeki c.328_330delT (p.Phe110Trpfs27*) mutasyon ile kesin tanı alan bir erkek hasta sunulmuştur. Bu olgu ile izole persistan proteinüri ile izlenen hastalarda düşük molekül ağırlıklı proteinürinin araştırılması ve Dent hastalığının ayırıcı tanıda düşünülmesinin önemi vurgulanmak istenmiştir.

Anahtar sözcükler: Dent hastalığı, hiperkalsiüri, izole persistan proteinüri

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Introduction

Dent disease is a rare genetic tubular disorder that was first described by Dent and Friedman in 1964. It is an X-linked recessive disorder characterized by the triad of low-molecular- weight (LMW) proteinuria, hypercalciuria, and nephrocalcinosis, and/or nephrolithiasis (1–4). It has been described in about 250 families up to the present time and its exact prevalence is not known. In addition to the classic triad, signs of Fanconi syndrome, hyperphosphaturia, polyuria, microscopic hematuria, aminoaciduria and rickets findings may be observed in the patients.

Sixty percent of male patients have a mutation in the chloride channel 5 (*CLCN5*) gene on chromosome Xp11.22 and 15% have a mutation in the *OCRL1* gene on chromosome Xq26.1. These genes encode chloride channel 5 and phosphatidylinositol 4,5 biphosphate phosphatase proteins, which have functions in the megalin and cubulin system in the proximal tubule. Mutant proteins lead to LMW proteinuria. Patients with mutations in *CLCN5* gene are classified as having Dent disease type 1, and patients with *OCRL* mutations are classified as having Dent disease type 2 (5, 6). The same mutation may lead to the occurrence of different phenotypes in different families depending on some genetic and environmental determinants. Although the disease is observed especially in males, carrier females may also have phenotypic characteristics. Chronic kidney disease (CKD) has only been reported in males up to the present time. End-stage kidney disease (ESKD) develops in the 3rd–5th decades in 30–80% of affected males. Although there is no specific treatment, it is thought that progression to ESRD may be slowed down with early diagnosis and early initiation of drugs that reduce proteinuria (2, 3). In this case report, we present a boy followed up with isolated proteinuria for a long time, and diagnosed as having Dent disease. Informed consent was obtained from the patient's mother.

Case

A five-year-old male patient presented to our clinic with proteinuria, which was detected incidentally about one year ago and persisted. In his personal medical history, there was no edema, hematuria, urinary tract infection, or known systemic disease. There was no history of parental consanguinity or a known renal disease (including nephrolithiasis) in family members. On physical examination, his body weight was 18.5 kg (50–75 thp) and height was 110 cm (50–75 thp). His blood pressure was 100/60 mm Hg and he had no peripheral edema. Serum biochemical tests were as follows: blood urea nitrogen (BUN): 10 mg/dL, creatinine: 0.49 mg/dL (glomerular filtration rate 105 mL/min/1.73 m^2), albumin: 4.6 g/dL. Electrolyte levels were normal. Blood gases revealed a pH value of 7.38 and a HCO3 value of 20.1 mmol/L. Urinalysis revealed a density of 1018 and trace protein was found in urine. However, significant proteinuria was found in the 24-hour urine (30 mg/m^2/h). Although renal ultrasonography (USG) was interpreted to be normal in another center, USG examination in our hospital showed medullary nephrocalcinosis. Hypercalciuria was found in 24-hour urine (5.9 mg/kg/day; N <4mg/kg/day). Aminoaciduria and increased β2 microglobulin level in spot urine (76 mg/L) were found in urinalyses performed in terms of tubulopathies. An ophthalmologic examination and hearing test were normal. Static renal scintigraphy (DMSA), which was performed to determine the presence of scarring in the kidneys revealed higher-than-normal background activity and bilateral decreased activity uptake in the kidneys (more prominent in the left kidney). Dent disease was suspected in the patient with medullary nephrocalcinosis, hypercalciuria, and low-molecular-weight proteinuria and then a DNA sample was analyzed in Bonn University in Germany. Genetic examination revealed a mutation defined as c.328_330delT (p.Phe110Trpfs27*) in the *CLCN5* gene. Enalapril and hydrochlorothiazide (0.2 mg/kg/day) treatment was initiated. Patient's mother, sister, and male cousin did not have proteinuria and their beta 2 microglobulin levels in spot urine were normal. Genetic analysis was planned for his sister and male cousin. In the follow-up, the patient's proteinuria decreased (10 mg/m^2/h) and hypercalciuria regressed up to 2.8 mg/kg/day. He is still being followed up in our clinic and his renal functions are normal. Informed consent was obtained from the patient's mother.

Discussion

Isolated persistent proteinuria is a difficult condition that is commonly encountered in nephrology outpatient clinics, and many conditions should be excluded in its differential diagnosis. With this case report, we wished to emphasize the importance of investigating low-molecular-weight proteinuria and hypercalciuria in patients presenting with isolated persistent proteinuria, and that proximal tubular disorders including Dent disease should also be considered, especially in boys.

The typical triad of Dent disease was present in our patient. However, case series published in relation with this disease have shown that this triad is absent in 25% of patients, and patients may present with isolated proteinuria alone. It has been reported that renal biopsy reveals findings including focal segmental glomerulosclerosis (FSGS) and interstitial fibrosis in some patients, and these patients are followed up with a diagnosis of FSGS and receive long-term im-

munosuppressive therapies. Therefore, it has been recommended that Dent disease should be considered in the differential diagnosis of idiopathic FSGS or asymptomatic proteinuria. In the differentiation of these two conditions, comparing urine protein/creatinine rates with urine albumin/creatinine rates is beneficial. In glomerular proteinuria, pathologically excessive protein passes to glomerular filtrate, and albumin constitutes an important portion of protein in urine. In tubular proteinuria, the reabsorption of proteins that pass into the glomerular filtrate under physiologic conditions, most of which have low molecular weight, is disrupted. In this case, mostly low molecular proteins are found in urine. If less than 40–50% of proteinuria originates from albumin, tubular proteinuria should be considered, and one of the conditions that lead to tubular proteinuria is Dent disease. If a routine urine examination performed using a urine dipstick reveals trace or 1+ protein in a patient who has more than 1 g proteinuria daily, tubular proteinuria should be considered because the reagent in a urine dipstick is sensitive only to albumin, and does not indicate other proteins in urine (7, 8).

Static renal scintigraphy is a method that is recommended to exclude renal scarring in the differential diagnosis of isolated proteinuria. Background activity was higher than normal on DMSA scintigraphy in our patient, and a reduction in activity uptake was found in the kidneys bilaterally. This appearance is a finding that is observed especially in pathologies associated with megalin cubulin system dysfunction in the proximal tubule. Normally, DMSA is predominantly reabsorbed in the proximal tubule after passing into the glomerular filtrate, just like LMW proteins, and indicates renal parenchyma scintigraphically by accumulating here (9, 10). In Dent disease, DMSA accumulates in other tissues because its tubular reabsorption is disrupted. Therefore, background activity is found to be increased. In individuals with normal glomerular function, Dent disease should be considered when background activity on DMSA is found to be increased (6, 9).

A mutation defined as c.328_330delT (p.Phe110Trpfs27*) was found in the *CLCN5* gene in our patient. Among patients with Dent disease described in the literature, 60% have a mutation in the chloride channel 5 (*CLCN5*) gene on chromosome Xp11.22, and 15% have a mutation in the *OCRL1* gene on chromosome Xq26.1 (5). Therefore, another disease that should be considered in the differential diagnosis in presence of LMW proteinuria, is Lowe syndrome, which is also known as oculocerebrorenal syndrome arising from a mutation in the *OCRL* gene. Its classic triad includes mental retardation, congenital cataract, and proximal tubulopathy. In Lowe syndrome, the findings of Fanconi syndrome (aminoaciduria, glucosuria, renal tubular acidosis) are observed more frequently compared with Dent disease, and hypercalciuria, nephrocalcinosis, and nephrolithiasis are rarer (5–7).

There are also different phenotypes with no mutation in both genes. Carrier females may be manifested with clinical findings because of X chromosome inactivation. The same mutation may lead to the occurrence of different phenotypes in different families depending on some genetic and environmental determinants, and findings may occur at different times and in different ways in individuals who carry a mutation in the same family. Therefore, screening relatives of patients, including women, is very important (2, 3). Measurement of β2 microglobulin and retinol-binding protein in urine is recommended for screening, and mutation analysis is recommended for definite diagnosis (6, 7).

In conclusion, Dent disease is a genetic disease that should be kept in mind in patients followed up with isolated persistent proteinuria. It is a rare disease, but early diagnosis is important because it leads to ESRD. Hypercalciuria and nephrocalcinosis are findings that give clues in the diagnosis of this disease.

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