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Dent's disease: A cause of urolithiasis to bear in mind

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Description

Under the term Dent's disease a heterogeneous group of X-linked recessive renal disorders is found. Depending on the gene involved, there are different types of Dent's disease: 1) patients with mutations in the Cyanogen Chloride (CLCN5) gene are those affected by Dent's disease type 1 (65% of the patients); 2) mutations in the Oculo Cerebrorenal syndrome of Lowe (OCRL) gene are present in 10%-15% of the patients affected and are responsible for Dent's disease type 2; 3) conversely, there is a group of patients representing around 25%-35% with no identifiable mutation and are classified as Dent's disease type 3 [1].

Being the most common gene affected, the pathophysiology of the mutations in the CLCN5 gene is the most well-known. This gene encodes a Cl−/H+ exchanger (ClC-5) present in the endosomes of the proximal tubule. Its mutations prevent the endosomes from keeping an internal acid pH. In consequence, the proteins filtered through the glomerular filtration barrier are not broken down, resulting in Low-Molecular-Weight Proteinuria (LMWP). Parathormone is one of the low-molecular-weight proteins filtered. Consequently, it activates the PTH receptors located in the distal part of the proximal tubule, increasing bone resorption directly and indirectly through 1,25-OH-vitamin D activation [2,3]. The resulting elevated bone resorption causes hypercalciuria and hyperphosphaturia [4].

Patients are usually diagnosed at pediatric age. Generally, they present LMWP, hypercalciuria, hyperphosphaturia, nephrocalcinosis or nephrolithiasis and progressive renal failure. Additionally, patients can have hematuria, hypophosphatemia, rickets, osteomalacia, growth restriction or short stature [5,6]. In order to help in the diagnosis, there are three criteria that need to be present: 1) LMWP; 2) hypercalciuria defined as >4 mg/kg in a 24 h urine collection or >0.25 mg Ca2+ per mg creatinine on a spot sample; 3) at least one of the other usual symptoms (nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, hyperphosphaturia, bone disorders or renal failure) [1,3]. Once we have the clinical suspicion, the identification of a mutation in the CLCN5 or OCRL1 genes confirms the diagnosis [3], but we cannot forget the 25%-35% of the patients who don't have any identifiable mutation [1]. When the diagnostic is confirmed, it is important to give correct genetic counsel to the patient's family, as there can be more than one individual affected in the same family.

Even though Dent's disease patients are usually identified in the pediatric age given its clinic and/or past family history, there can be milder cases that go unidentified during childhood [1]. That is the reason we cannot dismiss it in adulthood, and we must bear in mind this condition when facing an adult patient with recurring urolithiasis, a family history of urolithiasis,

LMWP and hypercalciuria with or without renal failure [7].

Currently, the focus of the clinical management of patients affected by Dent's disease is in preventing nephrolithiasis and renal function impairment [3]. In order to reduce hypercalciuria and, consequently, lowering the risk of nephrolithiasis and renal damage, thiazide diuretics are a good option because they increase calcium reabsorption in the distal tubule [8]. Additionally, we can also add potassium citrate because it is a chelate of urinary calcium and an inhibitor of calcium phosphate lithiasis crystallization [9], one of the main stone compositions of these patients (the other being calcium oxalate). However, we must remember that the cause of hypercalciuria is bone resorption, so another option in the treatment armamentarium is phytate due to its capacity to decrease bone resorption and to inhibit calcium phosphate lithiasis growth [10,11]. Even though the correct treatment is initiated, it is possible that the patient develops Chronic Kidney Disease (CKD). When they get to end-stage CKD, the best option is renal transplantation, as the disease doesn't recur after it [5].

Conclusion

In conclusion, Dent's disease is a group of heterogeneous X-linked recessive renal disorders characterized by LMWP, hypercalciuria, nephrocalcinosis, nephrolithiasis and progressive renal failure. It is usually diagnosed in childhood, but it can go unperceived until adulthood. On this account, we must bear in mind this disease when facing an adult patient with recurring urolithiasis, a family history of urolithiasis, LMWP and hypercalciuria with or without renal failure. Implementation of the correct treatment is of vital importance to avoid CKD.

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