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Genetic Aspect and Management of Nephrocalcinosis

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The term nephrocalcinosis has been used variously over the years to describe calcium deposition in the kidneys. Strictly speaking, the term should be reserved for generalized deposition of calcium phosphate (>95% of cases) or calcium oxalate (<5% of cases) in the interstitial renal parenchyma. Approximately half of children with nephrocalcinosis who present before the age of 5 years have an identifiable genetic disorder. Risk factors for genetic disease include early age of onset (usually not in fetal life), consanguinity, and association with multiple, bilateral, and recurrent nephrolithiasis. Two main radiologic appearances have been described, cortical nephrocalcinosis and medullary nephrocalcinosis. Cortical nephrocalcinosis is rare and often generalized to the entire kidney. In most cases, the cause is outside the kidney. Proximal tubular defects usually do not cause overt nephrocalcinosis. Most patients with nephropathic cystinosis, for example, tend to have hyperechogenic kidneys, but frank nephrocalcinosis is an exception. Similarly, nephrocalcinosis and nephrolithiasis are classically described in Dent disease and are reported in 40-70% of cases. Again, most patients have only diffuse hyperechogenicity, with occasional hyperechogenic spots in the medulla, unless they have been treated with high doses of vitamin D for hypophosphatemic rickets. More than 95% of patients present with medullary nephrocalcinosis with or without nephrolithiasis. When approaching the differential diagnosis of medullary nephrocalcinosis, the first step is usually to understand whether patients have been exposed to excessive amounts of vitamin D, either because they have been supplemented with high doses of vitamin D or because they have a genetic disorder that produces high levels of 1,25OH vitamin D. In the course of the differential diagnosis, it is important to consider a number of feedback interactions between calcitriol, PTH and FGF23 that regulate serum calcium and phosphate levels. A typical example are variants in the SLC34A1 or SLC34A3 genes, where phosphate leakage secondary to loss of function of the NaPi2a or NaPi2c transporters suppresses FGF23 and causes unrestricted activation of 1,25OH vitamin D. This result in hypercalcemia, hyercalciuria, and

nephrocalcinosis, while increased intestinal phosphate reabsorption secondary to high vitamin D levels tends to normalize serum phosphate. Thus, a disease that is due to a defect in phosphate transport has a clinical expression as a defect of calcium metabolism. Altogether, diseases caused by primary or secondary vitamin D excess are usually recognized by hypercalcemic hypercalciuric nephrocalcinosis with suppressed PTH, unless patients have had a history of vitamin D intoxication but are in the recovery phase when they present. Primary hyperparathyroidism should also be excluded in all patients with nephrocalcinosis. Genetic disorders involving the thick ascending limb of Henle or the connecting tubule cause nephrocalcinosis with normocalcemia and hypercalciuria. In some cases, PTH is elevated secondary to the negative calcium balance caused by hypercalciuria. Most patients are easily recognized if they have metabolic alkalosis (Bartter syndrome), metabolic acidosis (distal tubular acidosis), or marked hypomagnesemia (familial hypercalciuric hypomagnesemia with nephrocalcinosis). These conditions will be reviewed during the presentation and the differential diagnosis will be discussed.

Keywords: Nephrocalcinosis, calcium, phosphate, vitamin D, FGF23