Metabolic Undertones of Kidney Stones

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Nephrolithiasis is increasingly recognized in children and is associated with high healthcare costs and frequent need for hospitalization. Compared to adults, a metabolic etiology is evident in 33–93% children with urolithiasis, emphasizing the need for rigorous evaluation of dietary, environmental, genetic, and metabolic risk factors [1]. Careful and repeated biochemical evaluation of blood and urine is necessary to identify an underlying cause that might enable individualized therapy to prevent stone recurrence.

In the current issue, Ramya and colleagues report the etiology of nephrolithiasis in 72 patients managed at a tertiary care center [2]. Following comprehensive metabolic evaluation, hyperoxaluria, and idiopathic hypercalciuria were identified as the most common etiologies, affecting almost one-third of patients each. Idiopathic hyperuricosuria, staghorn calculi, and vitamin-D toxicity were uncommon causes. While genetic confirmation was not sought, inherited disorders, including cystinuria, idiopathic hypercalcemia of infancy, and urate transport defects were suspected in 8% of patients, not unexpectedly in a cohort where 40% of the families reported parental consanguinity. Overall, an attributable cause was found in 82% of patients, underscoring the value of systematic metabolic evaluation in pediatric patients with nephrolithiasis.

Two major limitations of this study are lack of genetic sequencing and focused dietary history. A precise genetic diagnosis of primary hyperoxaluria has important implications for management. The modestly elevated levels of oxalate excretion in this study (mean 65 mg/1.73 m²/day) might indicate either dietary or idiopathic hyperoxaluria [3]; however, primary hyperoxaluria was not ruled out. Hyperoxaluria results in formation of calcium-oxalate stones, which account for 30–58% of nephrolithiasis in series from India, Pakistan, and Iran,

but less than a quarter of those from Europe and North America [4–8]. The Indian diet, with frequent servings of tea and leafy vegetables, provides 6–20 times the oxalate content in Western diets [3]; further, its relative lack of calcium and protein is also lithogenic. This underscores the importance of a detailed dietary history, with specific attention to dietary content of oxalate and calcium.

Patients with hypercalciuria require thorough evaluation including measurement of serum and urinary magnesium, beta-2-microglobulinuria and thyroid profile, as in the present study. Occasionally, patients with variants in *ADCY10*, *SCL34A1*, and *CYP24A1* and those with incomplete distal renal tubular acidosis are misclassified as “idiopathic” hypercalciuria, if evaluation for hypocitraturia, provocative tests of urinary acidification, and genetic sequencing are not performed.

The recent application of comprehensive genetic screening to stone formers has led to fascinating insights into the etiopathogenesis of nephrolithiasis. Whole exome sequencing in 51 stone-forming families found a monogenic cause in 25% children and young adults, with higher yields (~70%) in children < 5-y-old, those with family history, consanguinity and/or associated nephrocalcinosis [9]. Given the high rate of consanguinity, family history in 40% and young age at presentation (median 5 y), genetic sequencing might have provided valuable insights in the etiopathogenesis of stones in the study by Ramya et al.

Kidney stones have a monogenic cause in 15–20% of pediatric patients, and are inherited in > 45% cases overall. Identification of a monogenic etiology might help identify associated phenotypes, enable prognostication and might facilitate individualized medical management to prevent recurrent stones. Hence, while metabolic evaluation provides

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useful insight into etiology in the majority of children with nephrolithiasis, confirmation by exome-based genetic sequencing is imperative to enabling definitive management and genetic counseling.

Declarations

Conflict of Interest None.

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