Renal calculi in children

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Abstract

An increasing number of paediatric patients of all ages with renal calculi are being seen in outpatient clinics worldwide. This is attributed to changes in environmental factors like diet, fluid intake and obesity. In children however, genetic and/or metabolic disorders are still the main reason for kidney stones. Next to hypercalciuria, which is generally considered to be the most frequent risk factor, other lithogenic or stone-inhibitory disorders like hypocitraturia or hyperoxaluria and a variety of renal tubular diseases have to be evaluated by urine and/or blood analysis. Non-specific symptoms like growth retardation, intestinal malabsorption or bone demineralization are to be considered not only to avoid further complications, but for diagnostic purposes. In preterm infants a high incidence of nephrocalcinosis is observed. These infants often have a combination of immature kidney function or medication that leads to relative hypocitraturia. Concise evaluation to diagnose the underlying patho-mechanism as early as possible is mandatory in all paediatric patients. In more than three-quarters of children a metabolic basis of urolithiasis/nephrocalcinosis will be found. Early treatment by reducing urinary saturation index by increasing fluid intake, by providing crystallization inhibitors, but also by disease specific medication prevents recurrent kidney stones and/or progressive nephrocalcinosis and therefore deterioration of renal function.

Keywords diagnosis; hypercalciuria; hyperoxaluria; hypocitraturia; nephrocalcinosis; paediatric urolithiasis; treatment

Introduction

A significant increase in incidence and prevalence rates of adult nephrolithiasis has been noted in the industrialized countries. This increase is believed to mostly relate to environmental factors like dietary habits, fluid intake and obesity (metabolic syndrome). Although this is gaining importance in the paediatric population, genetic, metabolic and anatomical causes are still the main culprits for childhood stone disease. Nonetheless, paediatric outpatient visits and subsequently hospitalization for kidney stone disease have also increased over recent years.

Around 80% of kidney stones contain calcium. Most consist of calcium-oxalate and metabolic disorders including hypercalciuria, hyperoxaluria and hypocitraturia are the most prominent risk factors for both nephrocalcinosis and nephrolithiasis.

Urolithiasis (UL) is defined as stones formed in the kidney, but localized anywhere in the urinary tract. The term nephrolithiasis (NL) is used for stones remaining in the kidneys. Nephrocalcinosis (NC) describes calcium salts deposited in the tubules, the tubular epithelium and/or the interstitial tissue of the kidneys. NC frequently is classified based on the anatomic area involved: the three subtypes of medullary NC are rated according the degree of increase in parenchymal echogenicity and are differentiated from cortical (e.g. in acute cortical necrosis) and diffuse nephrocalcinosis.

The incidence of UL in adults is approximately 1.5 % and the prevalence rate is said to be 5.2%. About 12% of men and 5% of women in industrialized countries will pass a kidney stone at least once in their life. The incidence of paediatric UL is estimated to be approximately 10% of that in adults. In around 15–40% of children kidney stones are incidentally discovered. Due to the high proportion of non-specific symptoms the real incidence is almost certainly higher. In the 20th century it was reported that one in 1000 to one in 7500 paediatric hospital admissions were related to UL. More recently a nearly five-fold increase in hospital admissions for paediatric nephrolithiasis has been observed.

Childhood UL affects all ages, but younger children more often present with renal calculi, older children with ureteral stones. The sex distribution has changed over time and the historical male predisposition for UL is no longer found. A more pronounced risk of stone disease is now found in women. A recent study analyzing the sex distribution in more than 2 million children hospitalized because of UL reported a changing sex distribution according to age: boys were more affected during the first decade (1.2:1 for 0–5 years, 1.3:1 for 6–10 years), while girls were more affected during the second decade of life (0.96:1 for 11–15 years, 0.3:1 for 16–20 years).

Underlying metabolic disorders and a higher lithogenic risk is frequently found in children, but not in adults. Early diagnosis of a metabolic abnormality is important as treatment can prevent recurrence of UL, which is seen in up to 39% of children. Specific lithogenic risk factors are observed in up to 76% of children and, in some countries, hypocitraturia appears to be the most frequent.

Known paediatric risk factors include genetic abnormalities in epithelial transport, metabolic disturbances, anatomical abnormalities and urinary tract infections. The increasing incidence of stone disease in adults, however, is much more based on environmental factors mainly reflected by diet, e.g. an increased intake of salt, animal protein, carbonated beverages and vitamin C. Changes in climate may also have had a significant impact on stone disease, at least in specific regions of the world.

Obesity is an important risk factor for UL. Up to 30% of paediatric patients with UL diagnosed between 2003 and 2005 were reported to be overweight (more than 90th percentile). Nonetheless, a genetic background is much more obvious in the younger population with a lot of genetic diseases having their onset already in childhood.

Lithogenic risk factors of stone disease

Hypercalciuria

Hypercalciuria is the most frequently found urinary risk factor for UL. Primary (or idiopathic) hypercalciuria, is traditionally divided into a renal and an absorptive subtype. Primary hypercalciuria is the most common cause of calcium-containing stones. In the renal subtype, an elevated fasting urinary calcium excretion is found. However, many paediatric patients cannot easily be classified.

Idiopathic calcium NL is considered a multifactorial disease characterized by a complex interaction of environmental and individual, or genetic factors. Genetic factors undoubtedly contribute to stone formation. In up to 50% of patients with

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idiopathic hypercalciuria a positive family history is found. Also, calcium excretion is positively correlated between parents and their progeny and between siblings, but not between spouses. Genetic-derived risks appear to be greater than diet-related risks. So far, genetic research has focused on monogenic disorders and autosomal dominant, recessive and X-linked inherited genetic disorders have been identified.

Conditions leading to elevated urinary calcium with normal serum calcium

Medullary NC and calcium phosphate stones are frequently seen in patients with distal renal tubular acidosis (d-RTA, Figure 1). Here, a high urinary pH, hypercalciuria and hypocitraturia combine to predispose the child to renal calculi. Medullary NC with or without cortical NC is also described in tyrosinemia, a rare disease (1:100.000 live births) which often is combined with impaired renal function, aminoaciduria, hypercalciuria and tubular acidosis. In Dent's disease I, a rare but extremely severe X-linked hypercalciuric nephropathy with tubular proteinuria, early progressive NC and renal failure occur.

Hypercalciuria also occurs after long-term administration of furosemide, dexamethasone or ACTH. Hypercalciuria is also found in several syndromes ie Bartter's syndrome, William's syndrome or can occur secondary to renal tubular damage (Wilson's disease, Dent II syndrome, Table 1). Other conditions known to lead to hypercalciuria are hyper- and hypothyroidism, Cushing syndrome, adrenal insufficiency and metastatic malignant bone disease. Acid–base disturbances associated with long-term ventilation and parenteral nutrition can lead to hypercalciuria.

Conditions with elevated serum calcium

Other clinical entities lead to hypercalcaemia and secondary hypercalciuria. Here, primary hyperparathyroidism, the most frequent cause of hypercalcemic hypercalciuria in adults, is rather rare in children. Hypervitaminosis D, e.g. based on the application of multivitamin preparations including vitamin D, or on vitamin D added to milk preparations, or even due to vitamin D prophylaxis in (preterm) infants, may induce hypercalcaemia and hypercalciuria (Table 1). An excessive intake of *vitamin A*, more than 10,000 units/day, may also lead to hypercalcaemia and can therefore induce hypercalciuria. Short-term immobilization reduces bone mass rapidly (~15–20%) and is also accompanied by hypercalciuria.

Hyperoxaluria

An increased urinary oxalate excretion (hyperoxaluria) is an important promoter of crystallization processes. Primary (endogenous oxalate overproduction) is distinguished from secondary causes (Table 1).

Primary hyperoxaluria: currently, three forms of primary hyperoxaluria (PH), which are rare, autosomal-recessive

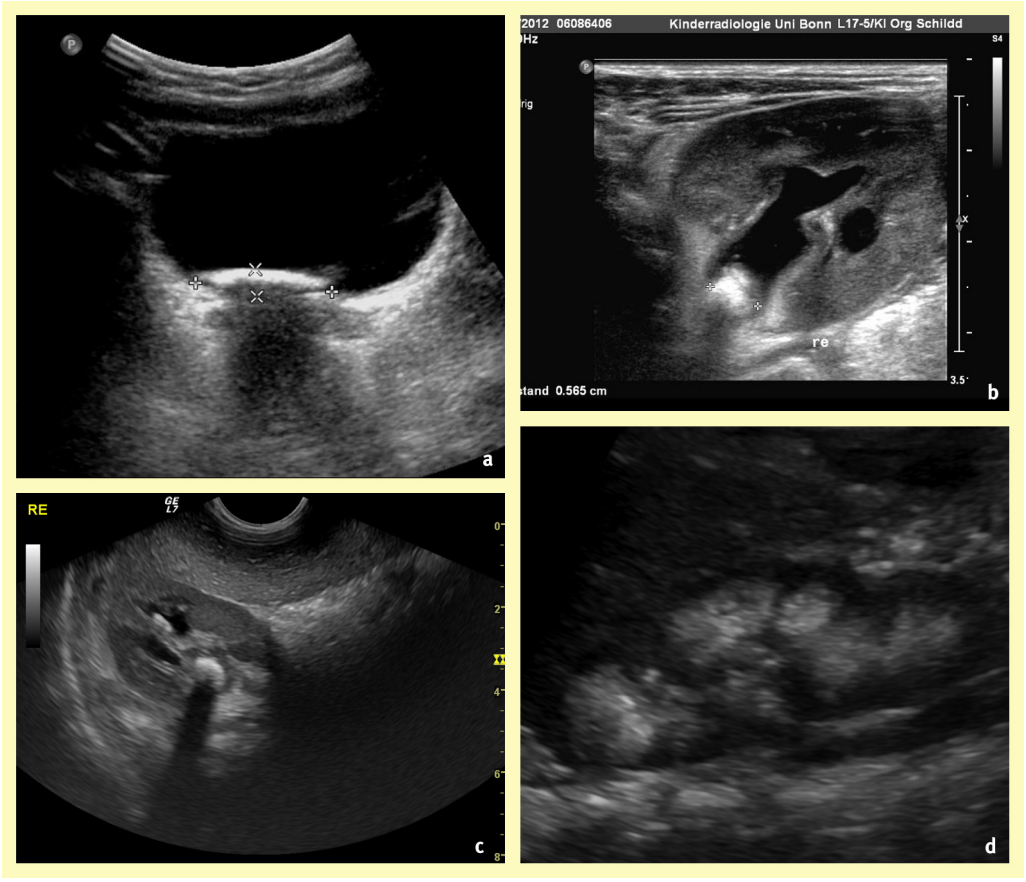

Figure 1 (**a**) Bladder stone in a 3-year-old girl with hypocitraturia, (**b**) kidney stones in a 20 months old girl with dystrophy and chronic urinary tract infections, (**c**) kidney stones in a patient with primary hyperoxaluria type III and (**d**) medullary nephrocalcinosis in a patient with renal tubular acidosis. Source: Images provided by Mark Born, MD, Department of Radiology, Division of Pediatric Radiology, University of Bonn, Germany.