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Metabolic disorders in kidney stone disease in children

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Abstract

Urolithiasis is not a rare disorder in children. Its etiology, incidence and localization vary by geographic region. It is an increasing problem, especially in developing countries. Metabolic abnormalities have been claimed to play a significant role in the kidney stone disease. Most of the studies confirmed that hypercalciuria, hypocitraturia are the most commonly identified metabolic disorder in children with urolithiasis. It is important to evaluate them to modify and prevent the stone recurrence.

Key words: nephrolithiasis, metabolic

Introduction

Urolithiasis is an increasing medical problem in developing countries. Paediatric kidney stone is a relatively rare condition in comparison to the high incidence in adults. The prevalence has been estimated between 0.1 to 5 % in the USA and Europe.[1] In Asia is reported from 1-5% to 13-15% in the USA [2]. For instance in Turkey urinary stone disease is seems to be endemic, about 17 % of all cases with nephrolithiasis were under 14 years. (kidney stones turkey. Nephrolithiasis has an extremely high prevalence in Saudi Arabia which is estimate to about 20 % with a probability to relapse up to 50 % during the life. [3] Admissions to a hospital because of renal stone disease varies in geographic regions, from about 0.001 to 0.1 % in the USA to around 7 % in Asia[4] [5]

The prevalence in recurrent nephrolithiasis changing through the lifetime, e.g., it was reported about 10 % in the first years, 35 % up to five years and about 50 % up to 10 years after the first episode of the formation. [6]

A lot of factors may contribute to urolithiasis, of which dietary, environmental factors, genetic, infection, anomalies of the genitourinary tract and the most important metabolic disturbances could have an essential influence in kidney stone formation.[7] It is considered with high morbidity despite low prevalence in children and it is associated with indicative rates of recurrence. [8]

In recent years, understanding the pathophysiology of nephrolithiasis in children improved greatly. Most young patients have underlying metabolic risk factors. It estimated that about 40 to 50 % of children have identifiable metabolic disorders. [9] It seems to hypercalciuria is the most prevalent abnormality in children. [1011]The other metabolic abnormalities include hypocitraturia, hyperoxaluria, hypomagnesuria, hyperuricosuria. To determine the etiology of stone formation is essential to evaluate urinary stone composition. The majority of calcium stones are composed of calcium oxalate (CaOx), about 75 %, calcium phosphate (50%), struvite (10-20%), urate (5 %) and cysteine (1-2%).[12] Rarely, stones mad also comprise xanthine , or 2,8-dihydroxyadenine. Moreover, most protocols recommend 24-hour urine collection as the gold standard to asses metabolic risk factors in stone disease patients.

The main mechanism is based on an imbalance between promoters and inhibitors of crystallization. To initiate a kidney calculi it requires the supersaturation of some ions in the urine. Total urine volume, the uneven proportion of promotors and inhibitors of crystallization, urine pH and total urine volume are the most relevant determinates responsible for solubility and crystallization. Highly acidic pH enhances calcium oxalate crystallization and promotes secondary nucleation of calcium oxalate by formation of calcium phosphate precipitates. Crystals can be formed in renal tubular fluid or in interstitial fluid.[13]. Promoters support the process of crystallization include: high oxalate, calcium, sodium, urate. The major inhibitors that prevent the process of stone formation include citrate, magnesium, pyrophosphate, some certain glycosaminoglycans, nephrocalicin, phytates and osteopontin. Moreover, citrates directly inhibit the crystallization, growth of kidney stones and reduce indirectly the saturation the calcium oxalate. [14] On the other hand, the coexisting of uric acid in the urine support calcium oxalate crystallization. [15] Only 1,2 % of children with urinary tract infection develop calculi. [16]

Mechanism of the kidney stone formation is still unclear, although the roots of this disease go back to Ancient Egyptians. In 1901, E. Smith found one of the first stone in the bladder from an almost 5000 years old mummy in El Amrah in Egypt. [17]The mechanism of stone renal formation include nucleation of crystals, growth and aggregation or second nucleation, fixation and further aggregation or second nucleation finally forming the clinical stone.[18]

Metabolic evaluation

Metabolic abnormalities can be found in majority of pediatric patients with nephrolithiasis.[1920]

Hypercalciuria:

Idiopathic hypercalciuria is the most frequent risk factors, being detected in approximately 30 % to 50 % of stone-forming children. [21] Mechanism of hypercalciuria is based on increasing intestinal absorption of calcium, decreased renal reabsorption of calcium, increases transfer calcium to bone and enhance urine supersaturation and crystallization.[13,22] In a study by Tefekli et all. found that hypercalciuria and hyperuricosuria were significantly higher percentage in adults than in paediatric population. Hypercalciuria is defined as calcium excretion of greater than 4mg/kg/d in children more than 2 years. Usually, a 24-hours urine collection is a gold standard to estimate daily calcium excretion.[23] For younger childs, the calcium to creatinine ratio is essential to estimate daily calcium excretion. Idiopathic hypercalciuria is the prevalent cause in children and adults. It is defined as an excess urine excretion of calcium with no underlying cause. To prevent calcium stone formation the thiazide diuretics have proven effective in reducing urinary excretion of calcium. Children with hypercalcaemic hypercalciuria should be investigated with hyperparathyroidism, hypervitaminosis D, sarcoidosis, malignancy, juvenile idiopathic arthritis or William syndrome. In patients with hypocalcaemia hypercalciuria, the possibility of hypoparathyroidism , autosomal, dominant hypocalcaemia hypercalciuria should be investigated. The majority cause is normocalcemic hypercalciuria, other conditions, such as Dent disease, Barter syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) or distal ren tubular acidosis (dRTA) should be excluded before establish appropriate diagnosis.

Familial primary hypomagnesemia with hypercalciuria and nephrocalcinosis FHHC, an autosomal-recessive disorder is characterized by renal magnesium and calcium wasting, nephrocalcinosis and progressive renal failure. The other symptoms include distal tubular acidosis, ocular abnormalities, and urinary tract infections. [24] The mutations in the gene CLDN16, which encodes for paracellin-1 9claudin-16) caused the FHHNC. [25]

Distal renal tubular acidosis dRTA is a rare kidney disease characterized by impairment of urinary acidification due to loss of bicarbonates. Different forms of this disease could be distinguished. The primary dRTA is characterized by hyperchloremic metabolic acidosis, severe nephrocalcinosis and or nephrocalcinosis associated with hypocitraturia and hypercalciuria. Type secondary could be caused by medication i.e., amphotericin B, some antibiotics or another disease e.g. systematic lupus erythematosus(SLE), Sjogren's syndrome or rheumatoid arthritis. [26]

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)is a rare autosomal recessive disorder, caused by a mutation in the SLC34A3 gene which encodes the sodium dependant phosphate cotransporter 2c. HHRH is characterised by hypophosphatemia, thus leading to increased 1,25(OH)2 vitamin D levels, hypercalciuria, short stature, muscle weakness or rickets. [2728]

Barter syndrome is rare, inherited autosomal recessive condition which is characterized by hypokalaemia, hypercalciuria, metabolic alkalosis and decreased serum magnesium levels. According to the age of onset, specific gene, severity it is classified types of Bartter syndrome. Mutations in the SLCA1, KCNJ1 and CLCNKB are responsible for Barter syndrome type I, II and III, respectively. In some cases, the cause of the disease has not been identified. The severity varies from mild to severe. The aim of treatment is based on correcting the imbalance of electrolytes, by using supplements or nonsteroidal anti-inflammatories (NSAIDs) and diuretic. [29,30]

Hypocitraturia:

Hypocitraturia is defined as less than 300mg/gm in 24-hour urine collection. Citrate are very important to inhibit stone formation. Citrate forms complexes with calcium and therefore lower the supersaturation of calcium oxalate, inhibit aggregation of some crystals and attachment of crystals to urinary epithelium.[31] In study Fallahzadeh et all detect in hypocitraturia in as one of the most common findings. In a study by Tefekli et all. hypocitraturia was the most common abnormality in paediatrics and adults group, 60,6% and 45,8 % respectively.[32] Some studies show that hypocitraturia alone or with hyperoxaluria are the most prevalent metabolic abnormalities in children with urolithiasis. [19,33]

Hypomagnesuria

Magnesium is a crucial inhibitor of crystallization and stone formation, thus inhibits the nucleation and growth of crystals, as well as aggregation. [34] In a study by Valavi et all. found almost 50 % of patients hypomagnesuria with a normal serum magnesium level. A group from Turkey concluded that decreased magnesium excretion was more commonly associated in children than in adults with nephrolithiasis. [35]

Hyperuricosuria

Is defines as urinary uric acid excretion more than 95% of normal values for age and sex. In a study by Valavi et all. found that 30 % patients had increased urinary acid excretion in 24 urine collection. The pathophysiological mechanism of uric acid based on of antagonistic influence on substances in the urine, and increasing binding calcium oxalate to cells .[14,36]Albait, uric acid stones are not common in pediatric population, children naturally excrete higher amount of uric acid. One study shows that in pediatric population there is no increasing risk for calculi due to excessive urinary uric acid excretion. [37]

Hyperoxaluria

In normal circumstances, 10-15 % of urinary oxalates originates from dietary intake. The pathomechanism of this metabolic disorder is focused on increased intestinal oxalate absorption, urinary supersaturation and formation of calcium oxalate crystals, increased dietary intake The inborn error of metabolism is known as hyperoxaluria. Type I is a rare condition inherited in an autosomal recessive trait. .[13,39]

Conclusion

Paediatric urolithiasis is an important medical problem, which have an increasing incidence in developing countries. Most patients have identified metabolic cause for stone formation. Multifactorial causes of stone disease in children should be detailed evaluated in children with lithiasis to enable appropriate treatment.

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