Urinary Stones in Neonates: Dilemma Between Urolithiasis and Nephrocalcinosis

Yeni Doğanlarda Üriner Sistem Taşları: Ürolitiyazis ve Nefrokalsinozis İkilemi

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ABSTRACT

Urinary stones are extremely rare in the neonatal population. Most of the urinary stones in the neonate contain calcium. Nephrolithiasis in the neonate may be as urolithiasis and/or nephrocalcinosis. The incidence of nephrocalcinosis is not yet clear and can be differ in many researches due to the etiology. On the other hand, the incidence of urolithiasis in childhood is almost 10% of that in adults. Especially in the first decade, it is more common in boys. It may occur with inherited metabolic changes such as hypercalciuria, primary hyperoxaluria or cystinuria. Stone formation can be effected by iatrogenic causes such as hyperalimentation (parenteral nutrition), diuretic therapy (furosemide, acetazolamide) that is especially in the bronchopulmonary dysplasia. The stone formation may occur due to anatomic or functional obstructions and infections of urinary system. Most of the urinary stones in the neonatal period are diagnosed as a nephrocalcinosis. However there aren't any exact differences between nephrolithiasis and nephrocalcinosis. Some authors suggested nephrocalcinosis is the initial step of urinary stone formation. On the other hand, the others purposed that both of them are different pathologies. In this review, we tried to summarized differences and similarities, in the context of urinary stones and the nephrocalcinosis in the neonates.

Key Words

Urinary tract, stone, nephrocalcinosis, urolithiasis, neonatal, newborn

ÖZET

Üriner sistem taşları neonatal dönemde çok nadirdir. Çoğu yeni doğan idrar yolu taşları kalsiyum içerir. Yeni doğanlarda nefrolitiyazis ürolitiyazis ve/veya nefrokalsinozis şeklinde olabilir. Nefrokalsinozisin insidansı henüz net olarak bilinmemektedir ve sebep olan etiyolojiye göre farklı bildirilmektedir. Öte yandan çocukluk çağında idrar yolu taşının insidansı erişkindekinin yaklaşık %10'u kadardır. Özellikle birinci dekadda erkeklerde daha sıktır. Hiperkalsiüri, primer okzalüri veya sistinüri gibi kalıtımsal metabolik değişikliklerle oluşabilir. Taş oluşumu hiperalimentasyon (paranteral beslenme), diüretik tedavi (furosemid, asetazolamid) gibi iyatrojenik sebeplerle özellikle bronkopulmoner displazilerde sık oluşur. Taş oluşumu anatomik veya fonksiyonel obstrüksiyonlar ve enfeksiyonlara ek oluşabilir. Yeni doğan döneminde genelde saptanan nefrokalsinozis bazı araştırmacılar tarafınca idrar yolu taş hastalığının başlangıç aşaması olarak kabul edilse de, öte yandan her iki patolojiyi ayrı kabul eden araştırıcılarda bulunmaktadır. Her iki patolojinin farklılıkları ve benzerlikleri net değildir. Biz de bu derlemede nefrokalsinozis ile ürolitiyazis arasındaki ikilemi özetlemeye çalıştık.

Anahtar Kelimeler

İdrar yolu, taş, nefrokalsinozis, ürolitiyazis, neonatal, yeni doğan

Introduction

The incidence of urolithiasis in childhood is almost 10% of that in adults (1). Urolithiasis and nephrocalcinosis are the two types calcification in the urinary tract. Urolithiasis is macroscopic calcification in the urinary collecting system. Urinary stones are composed of lithogenic crystal agglomerations and formed on the renal papillae by adherence to damaged renal epithelium. The imbalance of the activating factors such as high calcium/oxalate excretion and the inhibitor factors such as low citrate excretion determines stone forming. Nephrocalcinosis is microscopic calcification in the tubules, tubular epithelium or interstitial tissue of the kidney. It is classified according to locations are involved such as medullary, cortical or diffuse. Urolithiasis and nephrocalcinosis may occur together or separately. Theoretically, the composition and type (nephrocalcinosis or urolithiasis) of the deposits can be defined most effective with biopsy by pathologists. We summarized features of nephrocalcinosis and urolithiasis in the Table 1.

Prevalence rate of nephrocalcinosis was found 7-64% with a wide range in in the literature (2-12). Nephrocalcinosis is determined

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by repeated ultrasonography and may disappear in course of time (13,14). In the long-term studies, spontaneous resolution in course of time of nephrolithiasis for the preterm infants was reported 20-60% (8,15-19). Nephrocalcinosis will resolve in 75% of patients at 1-2 years of age. A prospective study suggested a 35% probability of nephrocalcinosis present at term to persist for at least 15 months and a 15% probability to persist for at least 30 months (19). It can be persistence among 10-25% was reported after 7 years (17,18). The long-term datas of nephrocalcinosis in preterm neonates have not been clear. Decreasing of renal function is due to lower gestational age or a lower birth weight was found for patients with nephrocalcinosis at term (16,20,21). Crystallization for nephrocalcinosis is common occur in immature kidneys of preterm infants. This can be explained by the 'heterogeneous nucleation' and 'low glomerular filtration rate' theories. In these theories, heterogeneous nucleation could occur earlier in preterm neonates than in adults and developing of nephron is continious process in this period so that preterm neonates have a low glomerular filtration rate (GFR) in fetal and neonatal life (17,22). Normally, the development of the kidney is centrifugal. Medullary nephrons in the deep develop earlier than the superficial cortical nephrons. Intrauterine growth retardation (IUGR) is associated with oligonephronia but not low birth weight. GFR increases due to development of the number and size of nephrons until the 36th week of gestation and reaches approximately 20 mL/min/1.73 m2 at 1 month of age in term. After the this period, GFR increases and reaches adult levels between 1 and 2 years of life. Plasma creatinine is high (1.1 mg/dL) at birth and then it decreases in the 1st week of life. In preterm infants, serum creatinine increases at 2-4 days of life and then decreases progressively, reaches to 0.4 mg/dL later and mostly at week 2 to 3 postnatal. Serum creatinine concentration may depend on maturation of the renal tubules (tubular reabsorption or secretion), the total muscle mass of the body and glomerular filtration rate. In the preterm infants, high serum creatinine levels may be depend on maternal serum creatinine (maternal kidney function, hydration, catabolic status, muscle mass), tubular reabsorption, underestimating of the true GFR in very low birth weight neonates with creatinine clearance, laboratory errors in the measurement of the serum creatinine levels (hyperbilirubinemia, hypertryglyceridemia, hemolysis, ketonemia), GFR overestimation (tubular secretion of creatinine or

secretion into the intestine), growth in muscle mass, dependence of age and gender, insensitivity of serum creatinine to small changes of GFR. Some reports have been suggested that nephrocalcinosis may predispose to glomerular and tubular dysfunction and the others have been proposed that prematurity alone leads to renal dysfunction. Kidney dysfunction may be depend on asphyx, feeding with formulas (best feeding with human milk), high renal solute load and negative water balance.

Diagnosis

Nephrocalcinosis seems to appear in the first years of life, which might be due to tubulopathies or metabolic disease of newborn. Nephrocalcinosis does not necessarily lead to renal calculi, nephrocalsinosis and urolithiasis may appear together in the same patient or may occur separately in the apparent absence of (macroscopic) nephrocalcinosis (23,24). Endoscopic examination of papillae may distinguish nephrocalcinosis or microcalculi which may be visualized as a hyperechoic spot of <3 mm in diameter on ultrasound or as a stone of a diameter <2 mm on a low enhanced computed tomography (CT) (25-27). Nephrocalcinosis are present mainly in the renal medulla. Medullary nephrocalcinosis can only be diagnosed when increased echogenicity appears in the area of the renal medulla by ultrasonography. It can be detected like white dots or white flecks that are echodense pyramids in the kidneys. Normally, the renal pyramids are hypoechoic areas in relation to the cortex. Echogenity can vary from small flecks of 1 to 2 mm, white dots larger than 2 mm, to completely echodense pyramids in the sonography. Two echogenic parallel stripes are considered to be the arcuate or branch arteries. Acoustic shadowing are not very common. For nephrocalcinosis, US was more sensitive than CT (96% vs. 64%), but CT was more specific than US (96% vs. 85%) in the rabbit research (6). US can use preferably to detect nephrocalcinosis, because it is a noninvasive, no need for sedation and sensitive method that does not involve radiation in infants. By 15 to 17 postmenstrual weeks half of fetal kidneys can be detected and the internal architecture of the kidneys can be reliably assesed on ultrasound examination and by 20 postmenstrual weeks 95% of fetal kidneys can be visualised. The supine position is suitable for preterm infants and the prone

Table 1. Features of the neprocalcinosis and urolithiasis		
FEATURES	Nephrocalcinosis	Urolithiasis
Appearance	Microscopic calcification	Macroscopic calcification
Location	Tubules, tubular epithelium or interstitial tissue of the kidney	Urinary collecting system
Follow-up	May disappear, spontan resolution	Spontan resolution not occur
Theroies of etiology	Inmature kidneys and low glomerular filtration rate	Activating and inibitor factors, stone formation theories
Risk factors	Prematurity, metabolic, medications, intoxications	Metabolic, medications, intoxications
Diagnosis	Hyperechoic spot of <3 mm in USG or <2 mm on a low enhanced CT	hyperechoic spot of >3 mm in USG or >2 mm on a low enhanced CT
Symptoms	Mostly asymptomatic	Symptomatic
Therapy	Conservative	Conservative or invasive

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position is the best choice for term newborns on the sonographic evaluation. Generally, image of the newborn kidneys is appeared to be similar or of slightly lower reflectivity than the liver. The best visualisation of the kidneys is obtained during the first few days of life before the child is established on gastric feeds. The other causes of increased medullary echogenicity in the preterm neonate are renal transient medullary hyperechogenicity, candidiasis, cytomegalovirus infection, infantile polycystic kidney disease or renal vein thrombosis. Ultrasonographic findings of transient medullary hyperechogenicity can be found in the first days of life of healthy full-term neonates and disappears within 6 to 14 days (28,29). The etiology of the transient medullary hyperechogenicity is not clear. Some authors suggest that aggregates composed of Tamm Horsfall protein (THP) cause the increased echogenicity. THP deposits within the renal calyces may look like nephrocalcinosis. Furthermore, the echogenicity of the renal cortex in neonates is physiologically increased, hence detection of cortical nephrocalcinosis can be difficult and may become evident only some weeks later when a rim of cortical calcification becomes visible. Cortical nephrocalcinosis is rare in infancy, but is described in acute cortical necrosis, renal vein thrombosis, cystinosis, chronic graft rejection, chronic glomerulonephritis and hyperoxaluria (30-33). Diffuse cortical nephrocalcinosis may already be detectable shortly after birth in patients with suspected primary hyperoxaluria.

Etiopathogenesis

Molecular mechanisms of stone disease are not clear yet. Stone formation by interstitial apatite plaques (Randall's plaques) on the papillae is typical of idiopathic calcium oxalate stone formers (34), crystal deposition in renal tubules is found in all stone-forming groups. Free solution crystallization is described to be typical of patients with cystinuria or secondary hyperoxaluria. Crystal formation in renal tubules and crystal retention in the distal tubules are main processes for the formation of nephrocalcinosis. Depend on increase of lithogenic factors or decrease of urine volume, urinary supersaturation leads to crystal formation in the renal tubules. If supersaturation does not exceed a certain level and duration, non-adherent epithelium, as well as tubular transport mechanisms controlling urine composition and adding crystal inhibitors such as citrate, magnesium and proteins, allow passage of supersaturated urine as well (35-41). When unhealty damaged epithelium occurs or failure of these protective tubular mechanisms, crystal retention is possible. This takes place in proliferating or regenerating cells in the distal nephron, which luminally express hyaluronan and osteopontin. Crystallization occurs due to proliferating and regenerating cells of preterm kidneys (especially depend on incomplete nephrogenesis, ischemia and nephrotoxic medications). Disrupting of the preventive physiological mechanisms for the crystal formation, adhesion can be occured by high amounts of a soluble crystal due to hyperabsorption (vitamin A/D excess, chronic inflammatory bowel disease, small bowel syndrome), overproduction (primary hyperoxaluria), deranged epithelium (infection, prematurity) and tubular transport defects (tubulopathies). Secondary heterogeneous nucleation of calcium phosphate or oxalate crystals in damaged tubular cells is the similar.

Aetiological factors of urolithiasis/nephrocalcinosis are classified as genetic pathologies, metabolic disorders, anatomical abnormalities, urinary tract infections and environmental factors (obesity, diet, fluid intake, metabolic syndrome) in pediatric patients. Prematurity is the main aetiological factor for nephrocalcinosis. Risk factors of nephrocalcinosis/urolithiasis are hypercalciuria (renal tubular abnormalities, abnormal handling of salt, over-production of prostaglandin E2, abnormal synthesis of 1,25-dihydroxy vitamin D3), primer or seconder (enteric) hyperoxaluria, hypocitraturia, hyperuricosuria, cystinuria, medication-intoxication (loop diuretics, calcium/vitamin D supplementation, carbonic-anhydrase inhibitors, topiramate, ethylene glycol, melamine, indinavir), tumor treatment (steroid treatment, loss of mineral from bone, reduced intestinal and renal calcium absorption) and urinary tract infections (Urease-producing bacteria). In the infancy, medullary nephrocalcinosis can develop as a result of renal tubular acidosis, administration of

Table 2. Causes of the renal calcification at neonatal intensive care unit (NICU)
Normocalsemic Hypercalciuric
Distal renal tubular acidosis
Bartter syndrome
Hyperprostaglandin E syndrome
Cushing syndrome
Adrenocorticotrophic hormone therapy for infantile spasms
Long term furosemide theraphy
Idiopathic hypercalcuria
Familial hypomagnesemia
Hypercalcemic Hypercalciuric
Hyperparathyroidism
Subcutaneous fat necrosis
Hypophosphatasia
Williams syndrome
Paraneoplastic Phenomenon
Idiopathic infatile hypercalcemia
Vitamin D intoxication
Normocalsemic Normocalciuric
Primary Hyperoxaluria
Short bowel associated Hyperoxaluria
Renal candidiasis
Rhabdoid tumors of the kidney
Dystrophic calcification
Long term acetazolamide therapy
Melamine contaminated formula

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furosemide, corticosteroid or vitamin D for preventing of rickets, hyperparathyreoidism or hyperoxaluria (42,43). Approximately 80% of the calcium and phosphorus accumulate in the fetus between the 25th postconceptional week and full term, with a peak between 34 and 36 weeks.

In the context of genetic factors, as neonates with a positive family history of kidney stones, those of male gender, and those of Caucasian race are more likely to develop nephrocalcinosis (9,10,44). Approximately 40% of children with urolithiasis have a positive family history, and most of the children have a metabolic factor of stone disease. Therefore, metabolic evaluation is necessary for neonates as older children (Table 2).

Risk factors for nephrocalcinosis in the neonatal period include low gestational age (<32 weeks), low birth weight (<1.5 kg), furosemide, dexamethasone, xanthines (theophylline, caffeine), aminoglycoside, male sex, length of assisted ventilation and oxygen therapy, length of hospital stay, nutrients (formulas and parenteral feeding) and fluid intake. High intake calcium, phosphorus, vitamin D, protein and ascorbic acid in the first four weeks are very important. Aminoglycoside therapy was also reported to contribute to renal calcification in preterm neonates (2,10,15). Premature kidneys have a long loop of Henle and hence a low urine velocity, resulting in crystal aggregation in the tubules (2). Nephrocalcinosis has been clearly associated with low gestational age and birth weight in many sutdies (4-7,10,44,45). Gimpel found a 1.65 fold increased risk per 100 g lower birth weight (44). Furosemide therapy with 410 mg/kg body weight per day was the strongest risk factor increasing the risk of nephrocalcinosis about the factor (45). Some studies identified furosemide therapy as a major risk factor, whereas others did not (4,10,11,46). The reduction of passive calcium reabsorption normally driven by sodium chloride transport leads to hypercalciuria and may be aggravated by a slower plasma clearance (47,48). Hypercalciuria itself was reported to increase the risk of nephrocalcinosis about 4.5 times per mmol/l increase of urinary calcium concentration. Hypercalcuria in preterm infants has also been associated with high dose steroid treatment, whereas other studies did not identify this as a risk factor (10,44,46,49).

The patients with nephrocalcinosis developed chronic lung disease (CLD) significantly more often. Both of metabolic and respiratory acidosis occur commonly in preterm infants, and risk of renal calcification is very high in the neonatal period. They are generally more immature and often need more of the etiological medications. Preterm infants with lung disease are reported to have decreased urinary citrate, which may predispose them to nephrocalcinosis. It was suggested infants who still required oxygen treatment in the neonatal period, had major risk for renal calcification. Ezzedeen et al. have reported oliguria (<1-5 ml/kg/hour) as a risk factor for renal calcification, found in 59% of their cases (21).

Therapy

Nephrocalcinosis is mostly asymptomatic but it is thought to predispose to urinary tract infection, renal colic, irritability and haematuria. If renal stones detected by ultrasonography, early postnatal evaluation is necessary to exclude obstructive lesions. If stones are prenatally detected, and solute/creatinine ratios and 24-hour urine collections can be made so that early diagnosis and specific therapy can be initiated. Early treatment with reducing urinary saturation of the soluble by increasing fluid intake and by providing crystallization inhibitors, as well as disease-specific medication, are mandatory to prevent recurrent kidney stones and/or progressive nephrocalcinosis, and consequently deterioration of renal function. Conservative therapy by increasing fluid intake and decrease sodium intake using low-sodium formulas are the first choice for neonatal urinary stone disease. Thiazide therapy and magnesium supplementation may be helpful in preventing further stone formation and may dissolve present stones. If there are multiple stones, a trial of potassium citrate should be undertaken. If 1,25-hydroxyvitamin D is elevated and urine phosphate is low, a trial of phosphorous supplementation is reasonable. This is designed to decrease hydroxylation of vitamin D and to decrease calcium absorption and excretion, thereby decreasing stone risk. If patient has normal urinary calcium/creatinine ratio and stone present, urine ratios for cystine/creatinine and oxalate/creatinine have to be check. If elevated oxalate excretion, it can be confirmed with a 24-hour urine collection for creatinine, oxalate, and calcium and obtain a random urine sample for creatinine, glycolate and glycerate. At this time, we can begin a trial of pyridoxine (250 to 300 mg/m2). Continue therapy until the results have confirmed or excluded hyperoxaluria. If oxalate excretion is elevated and there is no response to therapy, consider liver biopsy to elucidate the type of hyperoxaluria. Primary risks of urinary stone are recurrence, enlargement of current stone, obstruction, acute or chronic pyelonephritis in neonates. Extracorporeal shockwave lithotripsy (ESWL) is becoming the first treatment of choice in most cases, but this generally involves older children. Surgical management, endoscopic removal are rarely needed in the neonate.

More research is needed to elucidate aetiological factors, long-term effects and possible prevention or cure of nephrocalcinosis in preterm neonates. Long-term follow-up of blood pressure and renal function of prematurely born children, especially with neonatal nephrocalcinosis, seems warranted. Future research pertaining to prevention of nephrocalcinosis in preterm neonates is needed. After the delivery, newborn has to be checked with sonography as soon as posible, and after the first evaluataion periodically newborn has to be follow up for urinary stone disease. The etiology of nephrocalcinosis and long-term effects are not clear as yet, but some small studies show decreased estimated glomerular filtration rate. Nephrocalcinosis in the preterm neonates has been reported frequently and small studies suggest an unfavourable effect on renal function. Finally, urinary stones in neonates is dilemma between urolithiasis and nephrocalcinosis. There is need more researches and following studies about this topic.

Conflict of interest

There are no conflicts of interest.

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