UROLITHIASIS IN CHILDREN – ETIOPATHOGENY, CLINICAL AND PARACLINICAL DIAGNOSIS

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SUMMARY:
Urolithiasis in children is more frequent than anticipated, and remains often undiagnosed because of nonspecific or deceiving symptoms and signs. This paper aims to emphasize the causes and pathogenic mechanisms of lithogenesis, and to discuss the main clinical and paraclinical diagnostic features. Because metabolic causes of urolithiasis are frequent in children, the diagnostic assessment needs to be complex and complete, in order to detect underlying metabolic anomalies, which generate recurrent lithiasis or even progression to end stage renal disease. All children presenting abdominal pain or macroscopic hematuria must be investigated for urolithiasis. Personal and family history together with the physical examination are the first important steps in diagnosing this disease. Imaging of these children must be performed to locate the stones, but also to identify associated anomalies, congenital or secondary to urolithiasis. Often urolithiasis is not the disease per se, but an important symptom of another disease.

Key Words: urolithiasis, child.

LITIAZA RENALĂ LA COPII - ETIOPATOGENIA, DIAGNOSTIC CLINIC SI PARACLINIC.
Rezumat:
Litiaza renală este mai frecventă la copil decât se anticepează, și rămâne frecvent nediagnosticată, deoarece la un număr semnificativ de pacienți semnele și simptomele pot fi nesemnificative sau înșelătoare. Lucrarea de față își propune trecerea în revistă a cauzelor generatoare, mecanismelor patogenice ale litogenezei, alături de principalele elemente clinice și paraclinoșe de diagnostic pozitiv. Deoarece cauzele metabolice sunt frecvente la copii, evaluarea diagnostică trebuie să fie completă, pentru a depista anomaliiile metabolice care determină litiaza renală recurrentă sau chiar evoluție spre insuficiență renală cronicită. Toți copiii cu dureri abdominale colicative sau hematurie macroscopică trebuie explorati pentru urolitiase. istoricul familial și personal împreună cu examenul clinic sunt primii pași importanți în diagnosticarea acestei afecțiuni. Investigațiile imagistice pun diagnosticul, localizează calculii, dar identifică și anormaliile asociate, congenitale sau determinate de litiaza. De multe ori litiaza nu este boala în sine ci doar un semn important de boală.

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SYNOPSIS
Urolithiasis in children is more frequent than anticipated and remains often undiagnosed because of nonspecific or deceiving symptoms and signs. This paper is proposes to emphasize the generating causes and pathogenetic mechanisms, together with the principal clinical elements and preclinical diagnostic features.

Because metabolic disorders are frequent in children, the evaluation must be a complete one so that we are able to find the metabolic anomalies, anomalies that are responsible for recurrent urolithiasis or even a renal insufficiency. All children presenting abdominal pain or macroscopic hematuria must be investigated for urolithiasis. Personal and family histories along with the physical examination are the first important steps in

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diagnosing this disease. X-ray investigations enable us to diagnose, to locate the calculi but they also identify the associated anomalies, congenital or secondary to urolithiasis. In most cases urolithiasis isn’t the principal disease being just an important sign of a disease.

Urolithiasis is an affection characterized by the shaping of concretions / calculi at the pielocaliceal system and in urinary tracks, as a precipitation result of the substances dissolved and found normally in the urine. Nephrocalcinosis must be differentiated because it indicates the growing of the calcium content in the kidney, even though these two affections can coexist.

LITHOGENESIS

Urinary calculi have a crystalline composition fixed in an organic matrix, representing 2.5 – 10 % of the calculi weigh.

The organic matrix composition has different proteins (glycoprotein Tamm-Horsfall), microbial detritus, additions, coagulated fibrin, conjunctive fiber tissue, and substances coming out of the urinary tracks because of the inflammation or as a consequence of renal and urinary malformations.

The crystalline composition is represented by one or more of the following elements: calcium oxalate, calcium phosphate, ammonium magnesium phosphate, uric acid, cystine and xanthine.

The crystallization mechanism and calculi aging aren’t well-known. Salt precipitation occurs when the product of the ionic constituent activity bypasses a certain critical level, a process that is very difficult to analyze. Firstly it is difficult to determine in what proportion a solvent is emerged in an ionic form. For instance 30 – 60 % of the urinary calcium is found in an ionic form, the rest will form complexes with polyvalent anions like sulphates, phosphates, oxalates, citrates, being fastidious to determine their proportion. Secondly, it cannot be clearly established which salt precipitates the first one and which ionic product is relevant – for the calcium phosphate is most likely to be the octacalcium phosphate transforming itself spontaneously in hydroxyapatites less soluble. Through satiation with some components, micro crystal nucleation can be produced, abiding a process of aging and dimension growth with calculi development.(1)

1. Calcic lithiasis

The mechanisms responsible for the calcite calculi development are(2):

- Urine satiation with calculi forming calcium salts - idiopathic hypercalciuria, characterized by the normal calcium serum but with high urinary discharge, containing two main pathogenic mechanisms: high intestinal calcium absorption and low tubular reabsorption. The causes of the urine satiation with calcium salt are hypercalciuria absorption, renal hypercalciuria, hypercalcuiuria resorption (primary hyperparathyroidism), and hyperoxaluria.

- Hyperuricozuria in a normal urinary pH context – generates monosodic salt inhibitors – hipocitraturia (distal renal tubular acidosis, thiazide diuretics, enteric hyperoxaluria) and the hypomagnesaemia (dietetic disorders).

2. Non - Calcic lithiasis

Uric lithiasis – Hyperuricozuria in fewer than 5, 5 urinary pH contexts determines the precipitation of the uric acid in the urinary track (primary gout, Lesch – Nyhan syndrome, uricozuric drugs).

Cystine lithiasis – in the cystinuria the tubular reabsorption of the cystine is affected, with urinary cystine satiation and its precipitation calculi formation.

Infection lithiasis (ammoniac and magnesium phosphates) – in urinary infections by germs, synthesizing the ureasis (Proteus, Pseudomonas), produced especially because of a malformative substrate, through degrading the urea, urine alkalizing is made (where the pH is over 7, 5) with calcium phosphates and insoluble magnesium precipitation.(1,2)

LITHIASIS TYPE AND GENERATING CAUSES

1. Infection lithiasis

75% children with infection lithiasis are under 5 years old, with a maximum incidence at 2 years old, 80 % are boys and 93 % present urinary infection in the moment of diagnosis determination. The calculi are often situated in the superior urinary track, especially at the level of the renal pelvis and taking its shape. The left kidney is being more affected in these cases; calculi can be bilateral in 15 % of cases. In most cases (75 %) the Proteus germ is marked out, that’s why, every child with Proteus ITU must be explored for Urolithiasis. In calculi’s composition the organic matrix is being well represented and the inorganic component can be Arc (ammonium and magnesium phosphate) or apatite (basic calcium phosphate). Proteus through the ureasic activity,
determines the ammonium shaping by urea splitting and urinary pH growth, favoring calcium phosphate precipitation and growing the magnesium and ammonium ionic phosphate product.

In most of the cases, there is a malformative substrate, 35% are with RVU. Usually the ITU cases are treatment resistant and the clinical picture can be associated with lombalgia and hematuria. The calculi or fragments can be eliminated through urine, being in general of a light consistency resembling tooth paste.(3)

2. Calcic Lithiasis

In most of the cases, the calcium calculi are the representatives of an existent metabolic anomaly.

- **Hypercalcemia** – Hypercalcemia syndromes can determine in a child more of the Nephrocalcinosis than the Urolithiasis. The causes of the Hypercalcemia and Nephrocalcinosis or calculi at this age group are: hyperparathyroidism, vitamin D intoxication, prolonged immobilization, idiopathic Hypercalcemia, hypothyroidism, alcaptonuria, hypophosphatasia and tumors.

- **Hypercalciuria** – represents the Urolithiasis at children and sometimes it determines hematuria, possibly caused by microcrystalluria. There are considerable variations in calcium excretion but a urinary creatinine/calcium report over 0.74 mmol/mmol from the secondly collected urine in the morning suggests the presence of Hypercalciuria. Urinary calcium excretion is increased in all previously described hypercalcemic syndromes. Hypercalciuria with normal plasmatic calcium can emerge in idiopathic Hypercalcemia, the high calcium mobilization in the bones (immobilization, Cushing syndrome, bone neoplasia deposits) and in renal tubular affections (ATRD, Bartter syndrome, Wilson disease, X-linked genetically affections that associates lithiasis with renal insufficiency). The two types of idiopathic hypercalciuria – absorption and renal – can be differed by asking if the diet had a lack of calcium or an excess of calcium, the answer makes the distinction very important because the treatment in each case is different.

- **Acidification disorders** – in distal renal tubular acidosis (H+ ionic tubular excretion deficit) it’s the recurrent characteristic of renal calculi along with the metabolic hyperchloremic acidosis with normal anion puncture, sodium urinary loss, potassium, calcium and the affecting of urinary polyuria concentration. The citraturia is low and the combination between hypocitraturia, hypercalciuria and alkaline urine, leads to calcium salt precipitation. Calculi can coexist together with nephrocalcinosis, and sometimes the calculi are obstructive and a surgical treatment is needed.

3. Oxalic lithiasis

Around 10% out of the urinary oxalic acid emanates from diet; the rest is the final product of the glioxilat and ascorbic acid metabolism.

- **Primary Hyperoxaluria** – the I and II type – recessive autosomal affections, characterized by the high urinary oxalate excretion with forming recurrent calculi with calcium oxalate occurring in childhood, have a small and a sharp size associates hematuria and renal gripes, and, very often evolutes towards IRC at the young adult. Type I is the most sever, presenting an alanin-glioxilataminotransferase (AGAT) deficiency; type II presents itself with dehydrogenases D’Glyceric deficiency.

- **Enteric Hyperoxaluria** – strikes the children with terminal ileum affection by growing the oxalate absorption.

- **Idiopathic oxalic lithiasis** – most of the adults affected by calcium oxalate calculi don’t have hyperoxaluria because of the idiopathic hypercalciuria. This lithiasis type also occurs at big children.

4. Cystinuria

At the tubular level there is a genetic deficiency in transporting the dibasic amino acids; cystinuria is represented by the urinary calculi recurrent formation, usually large, round, situated at the renal pelvis level and calyceal multiple calculi.(4,5)

5. Purine metabolism disorders

- **Uric lithiasis** – uric acid calculi are formed in the condition of uric acid overproduction – leukemia or postchemotherapy lymphoma, primary gout (big children), Lesch – Nyhan syndrome (Hypoxanthine-guanine phosphoribosyltransferase: the babies can have renal insufficiency and the lithiasis can precede neurological display), type I glycochenosis. At some male patients there is a tendency of uric lithiasis without hyperuricemia and hyperuricozuria, sometimes with family aggregation and childhood expression. Acid urine facilitates the uric acid precipitation.

- **Dihydroxy adenine calculi** – adenine–phosphoribosyltransferase deficiency, with radiotransparent calculi formation.
**Xanthinuria** – rare disorder given by the xanthine oxidase deficiency, forms radiotransparent calculi and is insoluble in the acid urine.\(^{(6)}\)

**Clinical picture**\(^{(7,8,9)}\)
- Asymptomatic form – clinical symptoms are absent, the lithiasis is adventitiously uncovered by medical imaging explorations (by ultrasounds or radiologic investigations).
- Symptomatic form
  - Renal colic – lumbar and abdominal boisterous pain, sometimes with typical radiation towards genital organs, associated or disassociated with a bad condition, vomiting, polakidisuria, macro- or microscopic hematuria, followed by the calculi elimination. The association between lumbar pain and hematuria is found also in hydronephrosis or in some IgA nephropathy cases.
  - ITU – all children with ITU especially the ones with Proteus urinary infection or recurrent infections and treatment-resistant, must be explored in order to track down any sign of a possible Urolithiasis. Obstructive calculi together with infection could lead to pyonephrosis with renal tissulaire damage and severe clinical symptomatology.
  - Hematuria – children with hematuria must be investigated for Urolithiasis, even when an evident cause of hematuria exists. There is a resemblance between recurrent hematuria and hypercalciuria even in the absence of calculi formation, but the relationship between this syndrome and Urolithiasis isn’t conceivable.
  - Lumbar and abdominal dull pains also recurrent and atypical, could suggest Urolithiasis.
  - Acute urinary retention and the globe bladder can indicate a calculus.

**Paraclinical investigations**
- Renal ultrasound – all children with ITU must undergo an ultrasound examination in order to diagnose the urolithiasis or nephrocalcinosis. Even though the small calculi can go unobserved, the ultrasound is more sensible the conventional radiologic examination in diagnosing nephrocalcinosis, and can detect radiotransparent calculi.\(^{(10,11)}\)
- Abdominal radiography on “empty” – this procedure shows radio-opaque calculi.
- Intravenous urography and retrograde urethral – cistography – the presence of calculi dictates the conduct of a complete radiologic investigation. The urography locates the calculi exactly, shows the radiotransparent calculi, takes out of discussion vicinity radio-opaque images (calcified mesenteric ganglion, phleboliths, and coprolites), highlights the malformative substrate, and evaluates the urinary obstruction level and the secondary renal injury. Retrograde urethral – cistography shows the inferior obstructive uropathy and the urethral bladder backflow.\(^{(12)}\)
- CT and RMN scan – the computer tomography strives to replace the intravenous urography, considered until recently the golden standard in diagnosing the urolithiasis.\(^{(10)}\)
- Biological investigations:
  - Serum investigations: urea, creatinine, uric acid, creatinine clearance, serum ionogram, phosphor, basic and acidic parameters and glycemia.
  - Urinary investigations: summary exam for hematuria, leukocyturia, crystalluria, urine pH, urinary density and uroculture.
- Metabolic investigations:
  - The decision is made based on de clinical circumstances – sterile urocultures, calculi recurrences, nephrocalcinosis, older age, are the criteria that dictates metabolic exploration. On the other hand the urinary biochemical evaluation should be effectuated in all cases in the urolithiasis diagnose moment. All children with lithiasis must go through the cystinuria screening, because the treatment is a medical one. Urinary biochemical determinations from the urine/24 h must be preoperatory done. An urinary pH under 5, 3 obtained spontaneously or after ammonium chloride upload test, exclude ATRD, but if the urine is infected, especially with Proteus, it may be difficult to exclude this diagnosis. Radiotransparent calculi need complex investigations in a specialized laboratory in order to diagnose the anomaly in the Purine metabolism.\(^{(13,14,15,16)}\)
  - Urinary biochemical determinations out of the urine/24 h: calciuria, phosphaturia, uricuria, oxaluria, citraturia, glycozuria, aminoaciduria, pH and density, some of the urinary creatinine and weight reports.
- The calculi analyze
The detected crystalline elements through urinary microscopy could suggest the calculi composition. Calculi chemical analysis is necessary and important, using different techniques from the optical crystallography and direct chemical analysis to X-ray crystallography, infrared spectroscopy or electronic scanning microscopy.

Recent researches are being made for developing a CT micro-scan method in order to determine the vivo calculi composition.

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**REFERENCES**