MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE

DISTANCE LEARNING CENTRE

DEPARTMENT OF „NEPHROLOGY, HEMATOLOGY AND GASTROENTEROLOGY“

LECTURE № 4

FOR E-LEARNING IN „NEPHROLOGY“

FOR MEDICAL STUDENTS

TITLE: **NEPHROLYTHIASIS**

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PLEVEN, 2020

NEPHROLITHIASIS

Epidemiology

Nephrolithiasis (NL) has an annual incidence 7-21 cases of 10 000 persons and accounts 7-10 of 1000 admissions in the USA. There is no any sex difference in affected patients in Bulgaria.

The predominant age of onset is 3^{d} to 5th decade of life. Incidence is higher in the developed countries, probably as a consequence of increased animal protein intake. In underdeveloped countries NL is relatively uncommon and there bladder stones predominate.

Classification and characteristics of renal calculi are different. Most stones (80-90%) are *calcium oxalate* and their pathogenesis is idiopathic. The predominant *calcium phosphate* stones usually reflect alkaline urine and have specific causes as primary hyper-parathyroidism, renal tubular acidosis, alkali therapy, or milk-alkali syndrome. Noncalcareous stones - *uric acid, magnesium-ammonium phosphate* and *cystine* constitute the remaining 10-20%.

Calcium oxalate stones are most common, occurring alone in 35% and as a mixture with hydroxiapatite in 35%. Pure calcium phosphate stones (hydroxiapatite or brushite) are encountered in 10%. The most common noncalcareous stones are composed of struvite ($MgNH_4PO_4.6H_2O$) occurring in 10%. Stones of uric acid (10%), or cystine (1%), occur alone or as mixtures with calcium salts. Rare stones include sodium urate, xanthine, 2,8-dihidroxiadenine or triamterene.

Pathogenesis

Stone formation can be attributed to increased urinary concen-tration of crystalloids, decreased inhibition, or increased promoter substances. Stone formation begins with nucleation, the associa-tion of small amounts of crystalloids to form submicroscopic par-ticles. Nucleation generally occurs on existing surfaces, such as papillary epithelium. Urine must be saturated – the concentration product of constituent crystalloids must exceed the solubility pro-duct – to permit such association. Greater supersaturation (higher concentration of calcium and/or oxalate) favors nucleation. Stone growth occurs by aggregation or by crystal growth, the orderly movement of ions out of solution onto growing crystals.

Table. Urinary risk factors for calcium nephrolithiasis

Crystalloid concentration
• Hypercalciuria
• Hyperoxaluria

- Low urine volume

Promoters

- Hyperuricosuria
- Alkaline pH

Inhibitor deficiency

- Hypocitraturia
- Hypomagnesaemia
- Macromolecules
    - nephrocalcin
    - uropontin
    - Tamm-Horsfall protein

The role of inhibitors must be crucial. *Citrate* and *magnesium* form soluble complexes with calcium and oxalate respectively, which do not participate in nucleation. *Nephrocalcin* is a highly acidic protein of renal tubular origin. It binds to the crystal surfaces and inhibit aggregation and crystal growth. *Tamm-Horsfall* protein inhibits aggregation. There are abnormal types of nephrocalcin and Tamm-Horsfall protein, which have not got inhibitor activity. The role of these proteins is not yet measured in clinical practice.

Not all stones can be attributed to the metabolic risk factors. Several conditions predispose to stone formation because of *anatomical derangements*, including polycystic kidney disease, horseshoe kidney and medullary sponge kidney.

Risk factors for calcium NL

Calcium oxalate stones are the consequence of wide variety of *abnormalities*, including urinary tract abnormalities, low urinary volume, hypercalciuria, hyperoxaluria, and hyperuricosuria.

Some patients have habitually *low urine volume*. Calcium stone formation increases sharply, when urinary volume falls below 1100 ml/daily. Universal advice to increase water intake may account for so called stone clinic effect. Patients who formed no further stones keep increased urine output by 500 ml/d.

Hypercalciuria is defined, when daily excretion is more than 300 mg, or 4 mg per kg bodyweight. Hypercalciuria usually idiopathic occurs in 60% of stone formers. Renal tubular acidosis, sarcoidosis and familial hypercalciuric syndromes are rare causes of hypercalciuria. Hyperparathyroidism affected predominantly middle-aged and older women.

Hyperoxaluria. Oxalate is an end-metabolic product that forms poorly soluble complex with calcium. Normal excretion is 15-40 mg daily. Physicochemical considerations suggest that a small increase of urine oxalate has a larger effect on calcium oxalate saturation.

Hyperoxaluria may be due to increased intestinal absorption or increased synthesis (congenital **e**nzyme deficiency). High intestinal absorption may be due to high oxalate diet, calcium restriction, and intestine malabsorption.

Hypocitraturia. Normal citrate excretion is 300-900 mg daily. Citrate is an inhibitor of nucleation by forming insoluble complexes with calcium. Hypocitraturia may be due to intracellular acidosis, potassium /pъt**a**sjium/ deficiency, renal failure, chronic diarrhea /d**a**iъriъ/ or acetazolamide.

Hyperuricosuria is a risk factor for calcium stone formation, probably because uric acid acts as a surface for heterog**e**neous nucleation. Dietary restriction could suffice to ameliorate hyperuricosuria. Uric acid is 10-20 times more soluble at pH7 than at pH 5.

Infection stones. They consist of magnesium ammonium phosphate (struvite) and calcium phosphate (apatite). They form during urinary infection with urease production bacteria – Pseudomonas or Providentia species. These bacteria cleave urea to ammonia elevating urine pH to 8 or more, favoring precipitating of apatite and struvite. Bacterial infection is difficult to clear, as the organisms are inaccessible in stone interstices.

Cystine stones result from an unusual inherited disorder in which renal tubular reabsorption of cystine, ornithine, arginine and lysine is reduced. The solubility of cystine is 250-300 mg/l.

Symptoms

Symptoms of NLT are quite variable. Most often stones totally or partially obstructing the renal pelvis or the upper ureter are manifested on the affected side by flank and abdominal pain that is often colicky in nature, of extreme severity and accompanied by nausea and vomiting. When the stone is present in the middle to lower ureter, the pain often radiates downward toward the inguinal ligament and into the labia and urethra or testicle and penis. A stone located in the distal ureter can be manifested by urinary frequency or dysuria and thus be confused with symptoms of cystitis or urethritis. Passage of the stone yields immediate relief of pain. Gross or microscopic hematuria may be associated with any of these patterns of pain. Flank and back pain together with chills and fever are generally pr<u>e</u>sent when obstructing stones are complicated by infection. In some patients asymptomatic calculi are discovered when US, IVP or CT are obtained for other reason.

Diagnosis

The initial evaluation of a patient suspected of having NLT requires in addition to a thorough history and physical examination, a careful urinalysis including prompt examination of urine sediment. The detection of crystalluria may helps to identify the type of stone

present; hematuria is usual during the renal colic. A portion should be submitted for bacterial culture and the remainder for urinalysis.

US, Isotope nephrography, IVP and CT may individually or in combination be required to determine whether urinary stones are present, are radiolucent or radiodence, to determine their number, their size and location, what is their relation to urine flow.

Stone analysis should be obtained if a specimen is available. Too often the stone is lost in the toilet because the patient is given a container not enough big to contain the entire void volume. In other cases the stone is lost during unsupervised voiding after IVP as a consequence of the osmotic diuresis induced by r**a**dioc**o**ntrast material. Chemical stone analysis alone may give a definitive diagnosis. A simplified protocol may be used in single stone formers.

Treatment

In patients with *calciuria* are indicated fluid intake and dietary modification. Thiazides work in two directions: by causing extracellular fluid depletion and by increasing proximal tubular and distal tubular calcium reabsorption. Neutral orthophosphate reduces calcium reabsorption, increases proximal tubular calcium reabsorption, and increases urinary levels of pyrophosphate, an inhibitor of calcium phosphate nucleation. Cellulose phosphate is a nonabsorbed form of phosphate that binds calcium in the gut. In primary hyperparathyroidism parathyroidectomy is the optimal treatment.

Hyperoxaluria is treated by reducing dietary oxalates (tea, citruses, colas, spinach, rhubarb, peanuts and chocolates), adding magnesium supplements, prescribing pyridoxine. Enteric hyperoxaluria is treated with calcium supplements.

Urine alcalinization is the most effective treatment for most patients with acid uric stones. Indeed it is more effective than *allopurinol* (100-300mg/d.), which reduces /ridiusis/ urine acid excretion by about half. Target urine pH is 6,5-7,0 monitored by the patient with nitrazine paper. Urine acid stones dissolve during alkali therapy. Potassium citrate is the treatment of choice in dose of 30-60 mEq/daily in divided parts. The preferable drugs in Bg are *Soluran* and *Magurlit*, containing a mixture of sodium and potassium citrates and bic**a**rbonates.

Urological management of stones

Most stones (90%) pass spontaneously. It depends of size (length and width) of calculus. Ureteral stones 4 mm or less width are likely (70%) to pass within 1 year. Stones of 8 mm, or more in width are unl**i**kely to pass. Length of stone is less critical than width to determine the passage rate. Indications for urological intervention are obstruction, pain, fever, and ant**i**cipated failure of spontaneous passage. It is believed that complete obstruction requires

relief within 2 weeks: partial obstruction – in 4-6 weeks. Fever requires emergency decompression of urinary tract with retrograde stent or nephrostomy. Stones in the kidney or upper ureter may be treated with extracorporeal shock wave lithotripsy (ESWL). Ureteroscopy with basket retrieval or ultrasonic, or laser lithotripsy is successful in 95%.