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Review Article

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NEPHROLITHIASIS

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ABSTRACT

Urolithiasis and Nephrolithiasis refer to stones (calculi) in the urinary tract and kidney respectively. Kidney stones are common cause of blood in the urine and often severe pain in the abdomen, flank or groin. Stones are formed when there is a decrease in urine volume or an excess of stone forming substances in the urine. A number of different conditions can lead to kidney stones are gout, hypercalciuria, inflammatory bowel disease, some medications. Kidney stones are of different types: types of stones include calcium stones, uric acid stones, cystine stones and struvite stones, other substances may crystallize, precipitate and form stones. Several investigation procedures to find out the stones in the kidney. Some important investigation are urine culture and microscopy looking for infection, urine dip testing for blood and pH, renal functions and electrolytes, parathyroid hormone level, X-ray and renal ultrasound and helical CT scan. Management can either be done as an inpatient or an urgent outpatient basis, usually depending on how easily the pain can be controlled.

Keywords: Urolithiasis, Kidney, Calcium stones, renal ultrasound.

INTRODUCTION

Urolithiasis and Nephrolithiasis refer to stones (calculi) in the urinary tract and kidney, respectively. Renal calculi are formed when the urine is persaturated with salt and minerals such as calcium oxalate, struvite, uric acid and cystine. They vary considerably in size from small “gravel like” stones, to large “staghorn” calculi. The calculi may stay in the position in which they are formed, or migrate down the urinary tract producing symptoms along the way.[1] Renal stones are common, being present at some time in one in ten of the population, although a significant proportion will remain asymptomatic. Men are more commonly affected than women with a male to female ratio of 3:1. The peak age for developing stones is between 30-50 and recurrence is common.

GENERAL PATHOPHYSIOLOGY

Urinary tract stone disease is likely caused by two basic phenomena. The first phenomenon is super saturation of the urine by stone forming constituents, including calcium, oxalate and uric acid. Crystals or foreign bodies can act as nidi, upon which ions from the supersaturated urine form microscopic crystalline structures. The overwhelming majority of renal calculi contain calcium. Uric acid calculi and crystals of uric acid, with or without other contaminating ions, comprise the bulk of the remaining minority. Other, less frequent stone types include cystine, ammonium acid urate, xanthine, dihydroxy adenine and various rare stones related to precipitation of medications in the urinary tract. Other current theories also include renal tubular damage or dysfunction as an important component of the initiation of stone formation. The initial crystal agglomerations likely form in distal collecting tubules that drain into the renal papilla. As these masses grow, they gradually extrude into the collecting system through the papilla and eventually drop off to become free urinary calculi. The associated risk factors of obesity and Obesity and hypertension Diet High animal protein intake, Low fluid intake, Low calcium intake, High salt intake , Hot climate (or) occupation, Family history of renal stones, Medication, Anatomical anomalies in the kidneys and or urinary tract eg; horse shoe kidney, urethral stricture Gout, Hyper parathyroidism, Immobilization. Relative dehydration, Metabolic disorders which increase excretion of solutes eg: chronic metabolic acidosis, hypercalciuria, hyperuricosuria. [2,3]

TYPES OF STONES [4]

Calcium stones are most common. They are two to three times more common in men, usually appearing at age 20 to 30. Recurrence is likely. The calcium may combine with other substances such as oxalate (the most common substance) phosphate, or carbonate to form the stone. Oxalate is present in certain foods. Diseases of the small intestine increase the tendency to form calcium oxalate stones. Uric acid stones are also more common in men. They are associated with gout or chemotherapy. Uric acid stones make up about 10% of all stones. Cystine stones

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may form in persons with cystinuria. It is a hereditary disorder affecting both men and women. Struvite stones are mainly found in women as a result of urinary tract infection. They can grow very large and may obstruct the kidney, ureter or bladder.

MISCELLANEOUS STONE TYPES

- Protein matrix stones chronic infection (with struvite stones), end stage renal disease.
- Ammonium urate stones: laxative abuse
- Xanthine and 2, 8 dihydroxyadenine stones: inherited metabolic errors.
- stones composed of drugs: indinavir, Sulfadiazine, Triamterene

CALCIUM STONE DISEASE PREVALENCE[5]

Calcium stone disease is the most common form of nephrolithiasis and represents about 70% of all stone forming disease. It occurs most often in the third to fifth decade of life, more often in men than women.

Pathophysiology

In 60-70% patients, hypercalciuria will be present. In less than 5%, the hypercalciuria may be associated with hyperparathyroidism or sarcoidosis, with or without hypercalcemia. A minority of hypercalciuric patients have a renal leak of calcium (renal hypercalciuria) These patients have fasting hypercalciuria and slightly elevated levels of PTH and 1, 25 vitamin D. In some calcium stone formers the mechanism for the increased rate of calcium oxalate stones in the presence of hyper oxaluria. The hyperoxaluria is usually secondary to high dietary oxalate intake due to ingestion of foods or liquids containing large quantities of oxalate. Some of these foods and liquids include baked beans, collards green beans, rhubarb, tea, cocoa, peanut butter, and vegetable soup. In other cases, the hyperoxaluria occurs in the setting of gastrointestinal mal absorption, seen in patients with inflammatory bowel disease.

Risk factors for calcium stones[6]

1. Chronic low urine output.
2. Hyper uricosuria.
3. Low urine citrate, which occurs most often in patients with inflammatory bowel disease, chronic metabolic acidosis.
4. Renal tubular acidosis.

Signs and symptoms

Patients often present with episodes of flank pain that radiates to the anterior abdomen or even to the genitalia[7]. The pain is often severe and comes in waves. In some patients the renal stones are completely asymptomatic or may produce painless hematuria.

Diagnosis

Stone analysis is the surest way to diagnose calcium oxalate or calcium phosphate stones. Calcium containing stones are radio opaque on routine radiography but show up as bright objects on computed helical tomography without contrast. ltrasonography will detect all types of renal stones. If the stone is larger than 3 to 5 mm and the ultrasound is technically satisfactory. At present time, helical computed tomography without contrast is the procedure of choice for the initial radiographic investigation. All types of stones located anywhere in the kidneys, ureters or bladder will be demonstrated with this technology. Of the conditions associated with calcium stones, only pyelotubular ectasia (medullary sponge kidney) is better demonstrated by intravenous urography.

Therapy and outcome

In recurrent hypercalciuric stone formers, treatment should consist of high fluid intake, dietary sodium restriction, and thiazide diuretics. Thiazide diuretics reduce urinary calcium excretion by, Inducing extracellular volume depletion, which in turn causes increased renal sodium and calcium reabsorption, and By directly increasing distal calcium reabsorption. Dietary calcium restriction is not advised because of the potential for negative calcium balance and because a low calcium diet increases gastrointestinal absorption of oxalate and increased oxaluria. This increase in urinary oxalate can significantly raise the super saturation of the urine for calcium oxalate. This in turn increases the stone formation rate. In hypercalcemic stone forming individuals, the cause of the hypercalcemia should be sought and corrected. Correcting the metabolic acidosis in RTA and inflammatory bowel disease increases the urinary citrate excretion and lessens the urinary calcium excretion. [8]

URIC ACID STONE DISEASE PREVALANCE[9]

Uric acid stone disease is found in about 5% to 10% of stone formers. It is more common in patients with chronic diarrheal disorders and in those with hyperuricosuria. Most uric acid stone formers do not have gout or hyperuricosuria. Uric acid stones may also be partially composed of calcium oxalate, and some patients have both uric acid and calcium oxalate stones.

Pathophysiology

Uric acid stones occur especially in patients with very low urine pH (below pH 5.0) and in those with hyperuricosuria. Insome patients this very low urine pH is caused by a defect in renal ammonia secretion that results in less buffering of secreted hydrogen ion and lower urine pH. The very low urine pH is in some way related to the insulin resistance. Uric acid is very insoluble (15mg/dl) in urine at pH 5.0, but becomes significantly more soluble in urine at pH 7.0(150mg/dl). Any combination of low urine pH, concentrated urine(as seen in chronic diarrheal stages), and increased urinary uric acid excretion (as seen in patients with gout, chronic probenecid therapy, or high purine intake) make one at risk for uric acid stone diseases. These are rare congenital disorders of purine metabolism, ie Lesch-Nyhan syndrome, which are associated with uric acid stones and hyperuricosuria and hyperuricemia. Urate stones are radiolucent, but are visualized by both ultra sonography and noncontract helical computed tomography. If the uric acid is mixed with calcium oxalate, the stone will be radio opaque[10].

Signs and symptoms

Patients often present with episodes of flank pain that radiates to the anterior abdomen or even to the genitalia, as in calcium stone disease.[11] The pain is often severe and comes in waves. Often there is microscopic or gross hematuria.

Diagnosis

Uric acid stone disease should be suspected in any patient with typical symptoms of renal colic in whom the plain radiographs do not show a calcified stone. Urate crystals may be present in the urine, but occur in patients without stones as well. The urine pH will usually be less than 5.5. Stone analysis will provide sure diagnosis.

Therapy and outcome

Since the solubility of uric acid is greatly increased when urine pH is raised, treatment should consist of alkalinization of urine to pH greater than 6.5 with potassium citrate solution, 30 to 90 meq per day in divided doses, and by hydration. This treatment has been shown to reduce uric acid stone by 90%. Such treatment, given to a patient with small stones in the kidneys, may also result in dissolution of the stones.[12] When hyperuricosuria is also present, allopurinol can be used to reduce the serum uric acid level and thus reduce the renal excretion of uric acid. Restriction of animal protein is also recommended for patients with hyperuricosuria. Alkalinization of the urine with sodium bicarbonate or sodium citrate is not recommended because the sodium salts will increase calcium excretion and increase the tendency to form calcium oxalate stones.

STRUVITE STONE DISEASE PREVALENCE

Infection stones, also known as struvite or magnesium ammonium phosphate stones occur in about 10% to 12% of patients, more often in women.[13] They occur more often also in patients with spinal cord injury, neurogenic bladder, vesico urethral reflex, chronic indwelling foley catheters, and recurrent urinary infections, and in those with chronic obstruction of the upper urinary tracts.

Pathophysiology

Struvite stones occur only in the presence of urine persistently infected with urease –producing bacteria that split urea and cause persistently alkaline urine. Urea splitting bacteria include proteus (most commonly), Pseudomonas, klebsiella, some Escherichia coli and Staphylococcus species. Struvite stones are often branched (staghorn shaped) and large[14]. Because the stones contain ammonium they have a tendency to adhere to the uro epithelium, which tends to accelerate the growth of these stones in very short periods of time. Treatment requires eradication of infection with antibiotics and the removal of the bacteria- laden stones by some interventional technique.

Signs and symptoms

These stones may cause the typical symptoms of renal colic, but often they are discovered in the course of investigating a patient with recurrent urinary infections or in a patient with asymptomatic bacteriuria. Since these stones can grow to significant size, they are often found in the renal pelvis and infundibula of the kidneys.

Diagnosis

The diagnosis of struvite stones is suspected by finding large or branched stones in the kidneys of a patient with persistently infected urine. Stone analysis will confirm the diagnosis.

Therapy and outcome

Therapy must eradicate the urinary infection. Since the stones themselves are frequently infected with bacteria, the urinary infection cannot be erradicated without removing the stones as well. Thus, surgical removal of the stones accompanied by appropriate antibiotic therapy is necessary. Acetohydroxamic acid is a urease inhibitor. It has been used to prevent recurrence. Its effectiveness depends upon its presence in the urine; hence it has limited effectiveness in patients with azotemia. The use of this drug is further compromised because it has potentially serious side effects that include gastrointestinal upset, neurologic deficits and thrombophlebitis. Cystine stone disease occurs in less than 1% of all adult stone formers and in about 6% to 8% of children with nephrolithiasis.

Pathophysiology

Cystine stone disease occurs in individuals who have inherited autosomally recessive gastrointestinal and renal tubular transport disorders of four amino acids -cystine, ornithine, arginine and lysine of this cystine is the most insoluble in normally acid urine and thus precipitates into stones.

Signs and symptoms

The patient presents with symptoms of nephrolithiasis, often at a younger age than a person with calcium stone disease. The stones are radio opaque (ground glass appearance) and amber. Family history is often helpful (silbling may have the disorder).[15]

Diagnosis

Normal urine contain less than 20-30 mg/dl (<100mg/gm creatinine) of cystine. Urinary cystine excretion of greater than 250mg/gm creatinine in adults is clearly abnormal and is the usual amount found in patients with cystinuria. The examination of a concentrated, acidic urine specimen will often reveal the presence of the cystine crystals which are transparent and hexagonal. Cystine can be detected qualitatively by adding sodium nitroprusside to the urine and observing a purple red colour. Stone analysis is diagnostic.

Therapy and outcome

Treatment is directed at reducing urinary cystine concentration in the urine or by increasing urinary cystine solubility in the urine. The concentration of cystine in the urine is significantly helped by high fluid intake. There is a modest reduction of cystine excretion by reducing methionine (restriction of red meat, fish, poultry, and dairy products) in the diet and by dietary sodium restriction.[16] Alkalinization of the urine with potassium citrate to a pH of 6.5 to 7 is recommended. Sodium bicarbonate may be used for alkalinization, but the high sodium load increases cystine excretion. However, hydration and alkalinization alone are frequently ineffective at inhibiting recurrent stones. Thiol derivative are chelating agents. They contain sulfhydryl groups that can bind with the cystine and render it more soluble. Therefore these agents may also help to dissolve cystine stones as well as prevent their formulation. D-penicillamine and alpha mercapto-propionyl glycine are examples of such thiol chelating agent. Alpha mercaptopropionyl glycine is slightly more effective and produces fewer side effects. Captopril which also has sulfhydryl group has been used in limited studies with success.

Prevention

Recurrence of renal stones is common and therefore patients who have had a renal stones should be advised to adapt several life style measures which will help to prevent or delay recurrence. Avoid protein intake; usually protein is restricted to 60g/day to decrease urinary excretion of calcium and uric acid. A sodium intake of 3-4g/day is recommended. Table salt and high-sodium foods should be reduced, because sodium competes with calcium for reabsorption in the kidneys. Maintain calcium

intake at normal levels(lowering intake increases excretion of calcium oxalate) Avoid intake of oxalate contain foods (Eg; spinach, strawberries, rhubarb, tea, peanuts, wheat bran, chocolate).Drink regular cranberry juice; increases citrate excretion and reduces oxalate and phosphate excretion. During the day, drink fluids (ideally water) every 1-2 hours.[17] Drink two glasses of water at bed time and an additional glass at each night time awakening to prevent urine from becoming too concentrated during the night. Avoid activities leading to sudden increases in environmental temperatures that may cause excessive sweating and dehydration. Contact the primary health care provider at the first sign of a urinary tract infection.

REFERENCE

1. Brunner and suddarth's Text book of medical surgical nursing, Eleventh edition(page no:1589)
2. Goldfarb D S, Coe F l; Prevention of recurrent nephrolithiasis. Am Fam Physician 1999, 60:2269-2276.
3. Alan G Wasserstein, American Journal of kidney diseases Vol 45, No 2 February, 2005 , pp 422-428.
4. Auge B K, Preminger GM; surgical management of Urolithiasis. EndocrinOl metab clin north Am , 2002,31:1065-1082.
5. Kok D J; Clinical implications of physicochemistry of stone formation. Endocrinol metab clin north ARE 2002, 31: 8555-867.
6. Teichman J M; clinical practice, Accute renal colic from ureteral calculus. N Eng J Med , 2004, 350:684-693.
7. Asplin J R; Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin North Am 2002. 31:927-949.
8. Borghi L, Schianchi T, Meschi T, et al; Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Eng J Med 346:77-84.
9. Frick K K, Bushinsky D A; Molecular mechanisms of primary hypercalciuria. J Am Soc Nephrol, 2003, 14:1082-1095.
10. Goldfarb D S, Coe F L; Prevention of recurrent nephrolithiasis. Am Fam Physician 1999, 60:2269-2276.
11. Hamm L L, Hering-Smith K S; Pathophysiology of hypocitraturic nephrolithiasis. Endocrinol Metab Clin North Am 2002, 31:885-893.
12. Nicar M J, Hsu M C, Johnson T, Pak C Y; The preservation of urine samples for determination of renal stone risk factors. Lab Med, 1987, 18:382-384.
13. Pak C Y; Southwestern Internal Medicine Conference; Medical management of nephrolithiasis. A new simplified approach for general practice. Am J Med Sci, 1997, 313:215-219.
14. Sorensen C M, Chandhoke P S; Hyperuricosuric calcium nephrolithiasis. Endocrinol Metab Clin North Am, 2002, 31:915-925.
15. Tiselius H G; Medical evaluation of nephrolithiasis. Endocrinol Metab Clin North Am, 2002, 31:1031-1050.
16. Worcester EM: Stones from bowel disease. Endocrinol Metab Clin NorthAm , 2002 , 31:979-999.
17. Zerwekh J E, Reed-Gitomer B Y, Pak C Y; Pathogenesis of hypercalciuric nephrolithiasis. Endocrinol Metab Clin NorthAm, 2002, 31:869-884.