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RECURRENT NEPHROLITHIASIS – CYSTINURIA

INTRODUCTION

Nephrolithiasis is increasingly seen as a systemic disease that is associated with chronic renal failure and bone disorders and have an increased risk for coronary artery disease, hypertension, type 2 diabetes and metabolic syndrome. If left untreated it is a chronic disease with a recurrence rate of more than 50% in 10 years.

The prevalence of nephrolithiasis in the US has doubled in the last three decades, to 13% for men and 7% for women. The increase can be noted in most European countries and South-East Asia (2-5%). Overall, urolithiasis is more common in men, with a ratio of 3: 1. The rate of recurrent nephrolithiasis is 14%, 35% and 52% at 1, 5 and 10 years. The average time of re-formation of calculi in the tertiary center where they came patients with an average of four episodes of renal colic was less than 7 years. Interval in a number of different metabolic subgroup decreased from 4 to 2.5, with each subsequent calculus.

CASE STUDY

Thirty-seven year-old patient complained of pain in her left thigh with forward expansion on sudden standing up during hospitalization at the Clinic for Endocrinology for a more detailed examination in February 2012. In the 24 years established the right kidney stone, and because of hydronephrosis and anuria nephrectomy was performed in regional medical institution. The last three years, at least once a year, she had an anuria and lithoclast of calculus in the pelvic part of the left kidney was made in 2009 and 2011. In May 2009 was first examined by a competent endocrinologist when PTH was a slightly elevated 70.8 (15-65ng / l) with normal serum ionized calcium.

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On physical examination, she was short, slightly overweight (TV 160,5cm, TT 72kg, BMI 27.9), properly hydrated, with normal findings on the heart and lungs, HR 64/min, with diastolic hypertension TA 130/ 100mmHg. On the skin was pearly scar from nephrectomy from the right flank forward. There was easy tenderness of the left kidney essence of the lodge. The lower extremities were without edema. Other findings were unremarkable.

In biochemistry, unless mild hyperuricemia and hypercholesterolemia, other results together with complete blood count were within the reference ranges, as shown in Table 1. The urine was acidic reaction, on the basis of physical examination and pehametry, the proper specific gravity, without the crystals in the sediment, Table 2. Quantitative analysis of 24h urine distinct but sufficient volumes showed proper values of (dry and wet) creatinine clearance, proteinuria, sodium and potassium excretion, normal values of calciuria, phosphaturia, and excretion of oxalates, urates and citrates, Table 3. The hormonal analyzes pointed borderline PTH 66 (10-65ng/L), and featured a deficit vitamin D (15.3 ng / L). Thyroid function was normal. Analysis of the macroscopic appearance and chemical composition of calculus showed that this was a cystine calculi.

An abdominal ultrasound examination showed that the left kidney was compensatory increased, KK diameter 13cm, proper echogenicity and thickness of the cortex, clear cortex-medulla border, with signs of micro lythiasis without hydronephrosis. Given that the composition analysis showed it was a cystine calculi, the clinical symptoms and the age of the patient working diagnosis of cystinuria was set. The authors have tested a son and a patient at the Institute for Health Protection of Mother and Child "Dr Vukan Cupic". Based on the increased excretion of cystine 241,5μmol/mmol creatinine (1-17), lysine 561,4μmol/mmol creatinine (1-65), ornithine 187,9μmol/mmol creatinine (1-5) and arginine 340,7μmol/mmol creatinine (0-9) in a 24h urine of patient cystinuria was confirmed.

She got all the necessary advices for preventing the formation of stones (increasing fluid intake to 4-4,5l / d, alkalization urine with potassium citrate tablets, with monitoring of urine pH with test strips and potassium control) with Vigantol drops due to vitamin deficiency D as therapy.

DISCUSSION

Clinical and laboratory evaluation of patients with recurrent nephrolithiasis

According to the urolythiasis guidelines European Association of Urologists after the first episode of stone expulsion every patient should be placed in a group with low or high risk for repeated nephrolithiasis. For proper classification reliable analysis of the composition of calculus by spectroscopy or X-ray diffraction (the

gold standard) and basic analysis it is necessary. In addition, data about risk factors are important. Type of calculus is a decisive factor for further diagnostic tests. There are the following types of calculi: calcium oxalate and calcium phosphate (almost 80%), uric acid (10%), struvite (and infectious about 10%), cystine (0.7%), xanthine, 2,8-dyhidroxiadenin, originating from drugs and of unknown composition. Metabolic-specific evaluation is reserved only for patients with high risk. Metabolic evaluation includes the determination of the secretion of calcium, phosphate, oxalate, uric acid, citrate, sodium, magnesium and creatinine in the urine and 24 h urine volume. It is thus possible to establish increase of factors which promote the supersaturation or decrease of the factors that prevents it such as citrates, magnesium and volume. The specific metabolic evaluation requires two consecutive 24 hour urines. The alternative is to spot urine samples, particularly when collecting 24h urine difficulty as in small children. Spot samples have a limit because the results may vary in relation to the time of sampling, sex, age and weight of patients. It should be that at the time of specific metabolic evaluation the patient is without calculi, and it's been at least 20 days from expulsion or removal and 24h urine collection. In patients who began preventative treatment first control 24h urine should be collected after 8-12 weeks to assess the efficiency and modification in case of urinary parameters are normalized. Once sufficient to achieve normalization of the one-evaluation. The pathophysiological mechanism of calcium calculi is complex and varied, and includes a small volume of urine, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and abnormal urinary pH. Hypercalciuria definitely represents the most common metabolic disorder that may be the result of different mechanisms.

Cystinuria

Cystine stones consists of 1% to 3% of all renal calculi, and 6% to 8% of urolithiasis in children. Patients with cystinuria have a high rate of recurrent calculi and frequent urinary infections. Approach to these patients, begin with the identification of cystine calculi. Given that they are rare and they are usually not suspected until it analyzes the composition.

Cystinuria is an autosomal recessive hereditary disorder of epithelial transport and is characterized by excessive excretion of cystine and dibasic amino acids, arginine, lysine and ornithine in urine. It is caused by inadequate function of a specific membrane transport system in the brush border membrane of the cells of the proximal part of the right tubules and cells of the small intestine. The main clinical manifestation is the formation of urinary calculi due to the limited solubility of cystine. The solubility of cystine in urine is approximately 250 mg/L (1 mmol/L) up to a pH level of 7 while at pH 8 the solubility doubles. Solubility depends on the presence of other ions. The greatest solubility in the presence of CaCl, Mg and NaCl. The solubility depends of

presence of macromolecules in urine. After absorption it comes to disolution of two molecules of L-cystine to cysteine.

Dibasic AA inhibit the transport system which results in excessive amount of cystine, lysine, arginine and ornithine in urine in a classical form. In contrast, in an isolated cystinuria exists defect of isolated Km-system. In a normal jejunal mucosa there is one, common transport system for cystine and dibasic AA. It is an active transportation and depend on whether the defect is partial or complete there are different III variants of disorder after oral loading cystine. In general defect in the intestinal absorption of AA has minimal clinical significance.

Genetics and Clinical Presentation

Between 92-93. It was found that rBAT is expressed in cells of the S3 (pars recta) segment of the proximal tubule and small intestine at the luminal brush-border membrane. This gene is later named SLC3A1 in the Genome Database. To date, more than 60 different mutations have been described. One of the most common genetic alterations in SLC3A1 is called M467T, and most mutations tend to be population-specific. The M467T mutation is fairly common in Mediterranean populations. The prevalence of heterozygosity is approximately 1 case per 20-200 persons. Homozygous cystinuria affects 1 person per 15,000 population. Worldwide, the overall prevalence is 1 person per 7000 population. Cystinuria is more common in white persons. Cystinuria has no age predilection, although men are more severely affected. An incidence of 0.42 stone episodes for in males with cystinuria and 0.21 in females with the disease per annum has been reported. Cystine stones are common in the second or third decade of life. The peak age of first renal calculus is 22 years, although up to 22% of these patients develop calculi in childhood. Recurrent nephrolithiasis is a rule. Seventy-five percent of these patients present with bilateral calculi. Forming stones is usually the only clinical manifestation although in 10% of cases can be complicated by hypertension. Mentioned are sort stature, retinitis pigmentosa, hemophilia, muscular distofia and mongolism rare. Patients with cystinuria are at higher risk for nephrectomy of those who have calcium calculus. There is a high risk of kidney damage, fortunately ESRD occurs in less than 5% of persons with cystinuria. Cystine stones may be solitary or multiple, and often have coral appearance. Two-thirds of people with cystinuria have a pure cystine stones, one-third has mixed with calcium oxalate. Hypocitraturia, hypercalciuria and hyperuricosuria may be associated with.

Diagnosis

The urine of patients with cystinuria may have the characteristic odor of rotten eggs because cystine is one of the sulfur-containing amino acids. The simplest and

most widely used screening test is the microscopic examination of urine sediment. The presence of typical hexagonal crystals of cystine or petrol is pathognomonic finding. Microscopic crystalluria is located at 26% to 83% of patients. Disappearance of cystine crystals don't exclude diagnosis. Also, is a good index of treatment efficacy. Assessments of cystine excretion or solubility in the presence of cystine-binding thiol drugs are difficult. The sodium cyanide–nitroprusside test is a rapid, simple, and qualitative determination of cystine concentrations. Cyanide converts cystine to cysteine. Nitroprusside then binds, causing a purple hue in 2-10 minutes. The test detects cystine levels of higher than 75 mg/g till 125mg/g of creatinine. False-positive test results occur in some individuals with homocystinuria or acetonuria and in people taking sulfa drugs, ampicillin, or N -acetylcysteine. For individuals with positive cyanide-nitroprusside test findings, perform ion-exchange chromatographic quantitative analysis of a 24-hour collected urine sample. In cystinuria is more than 0.8 mmol/24 expressed only cystine. Best results are expressed per gram of creatinine. The upper limit of normal values for cystine is 18 mg/g creatinine for lysine 130 mg/g creatinine for arginine 16mg/g creatinine for ornithine 22mg/g. The functional definition of homozygotes is that this one person whose excretion is more than 250 mg cystine/gram of creatinine in urine 24 hours. Imaging methods include: native x-ray of the abdomen and urinary tract, IVP, spiral CT without contrast, renal ultrasound and foremost composition analysis by electron microscopy or x-ray diffraction.

Treatment

The essence of prevention in cystinuria hydration and urine alkalinization. This conservative treatment is a first line therapy in patients without calculus. The aim of hydration is to achieve a urine volume of 3l / day water intake of about 4-4,5l / day or 240ml (glass of water) every 8h, 480ml before bedtime and at least once during the night. It can be used mineral water rich in bicarbonate and poor in sodium (1500 mg HCO3 /L, max 500 mg sodium/L). Patients should use nitric tics to check specific weight of the urine with the maintenance of the target value of less than 1.010. Base urine prevents the precipitation of cystine calculi, and can help dissolution. The pH should be 7.5 to form a decomposition. At pH 8, however, comes to the formation of calcium stones which makes it necessary for patients to control their own urine pH should be between 7 and 7.5. Use of NaHCO3 is not recommended anymore. Potassium citrate is a alkalizing drug of first choice. Typically the dosage for adults is 60 to 80mmol/d in divided doses from 3-4 titrating to a pH of 7-7.5. Methionine is a metabolic precursor of cystine and that is why they have imposed the idea of a low-protein diet, but studies have not confirmed the success of a child. In case of conservative treatment failure drugs containing a thiol group and called chelating agents are being introduced. Since 1987 the beneficial effect of captopril in cystinuria

is described. Captopril is a thiol ACE-inhibitor of the first-generation and has been shown to produce a thiol of the cysteine-mixed disulfides, complexes which are 200 times more soluble than cystine. In particular, it is used in patients who are hypertensive. At a dose of 75 mg to 100 mg, reduces the excretion of cystine 70% and 93%. Penicillamine is a chelating agent of the first generation of cystine creates a soluble complex (50 times more soluble than the cystine), thus preventing the formation of calculus and potentially helps decomposition. There are three isomers D, L, DL, or only the D isomer has clinical significance. Doses of 1-2g/day are effective in reducing levels of cystine in the urine up to 200 mg/g creatinine. Alfa-merkaptopropionglicin is chelating agent of the second generation and has 30 times higher capacity of dissolution of cysteine than penicillamine. The main advantage of thiols is their low toxicity. In patients with gallstone decisions about further treatment is made in consultation with radiologists, nephrologists and urologists can be applied to next methods: extracorporeal shock wave lithotripsy, retrograde endoscopic lithotripsy and extraction, percutaneous nephrolithotomy, percutaneous nephrostomy with chemical dissolution and open surgery.

CONCLUSION

We have present a young patient with recurrent nephrolithiasis of solitary kidney and the risk of all complications of such a situation as a consequence of specific rare metabolic disorder. Prevention formation calculi is possible after a proper diagnosis. It is therefore important to determine the cause of nephrolithiasis.

Tabela 1. Biohemija i krvna slika

glikemija 4,5	AST 16	Er 4,46
urea 6,8	ALT 13	Hgb 138
kreatinin 63	ALP 44	Hct 0,41
ac. uricum 429… 410	gama GT 20	MCV 90,7
uk. bilirubin 18,8	CRP 0,5	Tr 212
uk. proteini 69	Na 140	Le 4,57
holesterol 6,24	K 5,2	SE
HDL 1,36	Ca 2,50 ... 2,50	
LDL 4,12	Ca^{2+} 1,21 ... 1,09	
trigliceridi 1,68	PO_4 1,10	
	Mg 0,86	

Tabela 2. Urin

bistar	žut	pH 5 (pehametrija)	spec. težina 1,016
sediment	2-3 leukocita	retke ep. ćelije	malo bakterija

Tabela 3. Kvantitativne analize urina

dU 2300 ml		dU 1700 ml
kreatinin 6,58 mmol/l	CCrm 113,88 ml/min	ac. urricum 2424 pmol/l 4120,8 pmol/d
	CCrs 112,76 ml/min	oksalati 0,14 mmol/l 0,24 mmol/d
proteini 0,05 g/l	Proteinurija 0,15g/d	citrati 1,45 mmol/l 2,46 mmol/d
Na^+ 67 mmol/l	natriureza 154,1 mmol/d	
K^+ 21 mmol/l	kaliureza 48,3 mmol/d	
dU 1000 ml		
Ca^{2+} 4,33 mmol/l	kalciurija 4,33 mmol/d	
PO_4 19,9 mmol/l	fosfaturija 19,9 mmol/d	

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