Cystinuria is an autosomal-recessive disorder with the code number of 220100 in Mendelian Inheritance in Man (MIM) online database of human genes and genetic disorders. It is characterized by tubular defect in the reabsorption of cystine and dibasic aminoacids. The disease has a frequency of 6-8% among children with renal stones. Without preventive measures, patients suffer from recurrent stone formation. Until recently, treatment of cystinuria has been limited to prevention of stone formation, by intensive hydration and urine alkalinisation and captopril. Various drugs have been used but their efficacy and safety remains controversial. A 7-year old girl with severe cystine urolithiasis is described with the objective of highlighting the therapeutic efficacy of captopril in resolving lithiasis as well as in preventing new stone formation.

Case report
A 7-year-old girl was referred to our hospital with persistent dysuria and non-specific abdominal pain. Her mother reported that, she had noticed the passage of a stone during voiding 20 days before. The patient’s past medical history was unremarkable, while there was a positive family history for renal lithiasis from second degree relatives from both sides of the families.

On admission, the child’s physical examination was normal. Regarding laboratory findings at presentation, routine hematological and biochemistry profiles, acid base balance, C-reactive protein and erythrocyte sedimentation rate were normal. Urinalysis revealed numerous red blood cells per high-power field on microscopic examination, in the absence of proteinuria. Urine analytes such as calcium, oxalate, and uric acid were within normal ranges. The urine culture was negative. Urine aminoacid analysis revealed increased levels of cystine, ornithine, lysine and arginine.

Imaging studies, including plain abdominal films, ultrasonography and intravenous pyelography demonstrated bilateral large radiodense coralliform calculi in both kidneys (Figure 1). This finding was related to
Hydronephrosis and obstruction of the major calyx of the left kidney and smaller size of the right kidney with thickness of the cortex. 99mTc-Dimercaptosuccinic acid renal scan (DMSA) revealed abnormal left kidney and small right kidney, with differential renal function of 82% and 18% respectively.

Due to the obstruction, an urologist evaluated the patient and percutaneous pyelolithotomy on the left side was performed. Chemical analysis of the calculi revealed cystine.

Diagnosis of cystinuria was based on the elevated concentrations of urine cystine and dibasic aminoacids, as well as the presence of cystine in the stones. Molecular analysis showed homozosity for the mutation S379R of the SLC7A9 gene of cystinuria.

Medical treatment was initiated with sodium bicarbonate to achieve urine alkalinization to a pH of 7.0 and captopril in a dose of 0.5mg/kg/day. Moreover, it was suggested that she maintained a high fluid intake and a low-sodium diet to reduce cystine excretion. Thereafter the follow-up of the patient was based on physical examination, laboratory findings, including routine hematology and biochemistry, acid base balance, urinalysis, serial radiological and nuclear studies to examine renal function, the presence and degree of urolithiasis or obstruction. One month later ultrasound findings showed residual calculi in the calyces of the middle and lower pole of the left kidney. Afterwards, a total of 4 sessions of extracorporeal wave lithotripsy (EXWL) every other month took place on the left side. Diuretic renography 99mTc-mercaptotriglycylcine was performed 8 months after diagnosis and revealed a large right kidney with good function (79%) and a smaller left kidney with poor renal blood flow and function (21%). Serial ultrasound and plain abdominal film studies were performed during EXWL sessions, at 12 and 18 months after diagnosis. The radiographic images of lithiasis on the left kidney were improved, due to EXWL, as was expected. The finding on the right side, where no intervention had taken place was remarkable in, that stone formation was less apparent showing gradual improvement and 18 months after medical treatment both kidneys showed no indication of the presence of lithiasis (Figure 2). Today, 30 months after medical treatment, cystine’s concentration in urine at pH 7.5 is 528μmol/l, which is well bellow the threshold for solubility of cystine (1250 μmol/l).

Discussion

Cystinuria is characterized by excessive urinary excretion of cystine, lysine, ornithine and arginine. The patients present with lithiasis as, the very low cystine solubility (1250μmol/l at a pH of 7.5) in urine results in cystine stone formation in homozygous patients and sometimes heterozygous. Lysine, ornithine and arginine do not form urinary stones.

Cystine stones are traditionally quite hard and often resistant to EXWL, and percutaneous surgery is indicated. Similarly, our patient initially underwent percutaneous pyelolithotomy for removal of the left side calculus. Additionally multiple attempts of ESWL at stone disintegration were necessary. Medical preventative treatment is based on high diuresis throughout day and night, urine alkalinization up to pH 7.5 by means of sodium bicarbonate or potassium citrate and low sodium diet to reduce cystine excretion. Treatment with sulfhydryl compounds, that convert cystine to a more soluble disulfide, is usually important. Such agents are D-penicillamine, which has serious adverse events in 50% of patients, including nephrotoxicity, and mercaptopropionyl glycine with less common renal and hematological reactions. Captopril is another sulfhydryl agent, which has been proposed for treatment of cystinuria lithiasis, since Sloand and Izzo first reported in 1987 a 70% reduction in cystine excretion with captopril. Furthermore Perazella and Buller reported a marked decrease in cystine excretion in two patients, including a decrease from 3.050 to 166 mg/day with captopril. In contrast, Coulthard et al observed only a small decrease in cystinuria in nine adult patients. In our case, captopril had excellent results. Such conflicting results suggest that besides the formation of highly soluble captopril-cysteine disulfides, captopril may act in other ways, such as interfering with amino acid metabolism or transport.
Follow-up is based on biannual radiographic findings. Efficacy of treatment should be monitored by measurement of urine density, pH and determination of 24-h free cystine excretion. In our case, captopril had excellent results leading to complete dissolution of the right side staghorn calculus after 18 months treatment. After a follow-up of 30 months the patient remained stone-free and his cystine concentration was 528μmol/l, indicating good metabolic control.

Screening for cystinuria is proposed for all high-risk relatives of affected patients. Our patient was homozygous for the mutation S379R of the SLC7A9 gene. Her parents were both heterozygotes, whereas no mutations were found in her sister. As cystinuria is a single gene defect, we can hope that, with genomic and proteomic advances, corrective intervention for the genetic anomaly may be available in the future.

In conclusion, considering that ESWL, ureteroscopic lithotripsy or open lithotomy are urologic procedures with sometimes serious side effects in the developing kidney, it is important to establish the efficacy of a medical agent, without serious adverse events, such as captopril, in children with cystinuria. Our experience shows that captopril can be useful in the prevention/treatment of cystine urolithiasis in children.

References