Evaluation of Children with Cystine Stones: A single-Center Experience

Sistin Taşı Olan Çocuk Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Cystinuria is a rare genetic disorder. Many patients suffer from significant recurrent urolithiasis, repeated surgical interventions, and the risk of progressive renal impairment. In the current study, the outcomes of patients with cystine stones were investigated.

Material and Methods: A total of Twenty-six cystinuria patients with cystine stones, aged between 3 months and 18 years, in our Pediatric Nephrology Department, were retrospectively analyzed.

Results: The mean age of patients at diagnosis was 45.2±45.5 months and 88,5% were male. Sixteen (62%) children had recurrent urinary tract infections. Only 10 (38%) patients showed additional metabolic abnormalities. The urinary pH had significantly increased with treatment and the number of stone recurrence was lower in the patients with urinary pHs ≥ 6.5. There was a significant positive correlation between the last-visit serum creatinine level and the number of surgical interventions. There was no significant correlation between the last-visit eGFR and the number of surgical interventions. On the other hand, eGFR values decreases as the total number of surgical interventions increases. No stone events were observed at the end of the follow-up period in 10 patients (38%) and the stone events per patient-year were 0.36 for all patients. Four patients with low eGFRs at the beginning of the study get normal with treatment after the follow-up period.

Conclusion: Cystinuria has significant morbidity if not controlled properly. Despite all treatments, it should be kept in mind that renal impairment may develop in cystine stones with cystinuria and surgical treatment should be planned by considering minimally invasive options.

Key Words: Child, Cystinuria, Urolithiasis, Kidney stones

ÖZ

Amaç: Sistinüri nadir görülen bir genetik hastalıktır. Birçok hasta, önemli ölçüde tekrarlayan ürolitiyazis, tekrarlayan cerrahi müdahaleler ve ilerleyici böbrek yetmezliği ile karşı karşıya kalmaktadır. Bu çalışmada sistin taşı olan hastaların sonuçları değerlendirildi.

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Gereç ve Yöntemler: Çocuk Nefroloji Bölümümüzde, yaşları 3 ay ile 18 arasında değişen, sistin taşı olan toplam 26 sistinürili hasta retrospektif olarak incelendi.

Bulgular: Hastaların, tanı anındaki ortalama yaşı 45.2±45.5 aydı ve % 88.5'i erkekti. On altı (% 62) çocukta tekrarlayan idrar yolu enfeksiyonu vardı. Sadece 10 (% 38) hastada ek olarak diğer metabolik anormallikler mevcuttu. Tedavi ile idrar pH'sının anlamlı olarak arttığı saptandı ve idrar pH ≥ 6.5 olan hastalarda taş tekrarlama sayısı daha düşük bulundu. Son-geliş serum kreatinin düzeyi ile cerrahi müdahale sayısı arasında anlamlı bir pozitif korelasyon mevcuttu. Son-vizit eGFR ile cerrahi girişim sayısı arasında anlamlı bir ilişki bulunmazken, toplam cerrahi girişim sayısı arttıkça eGFR değerleri azalmaktaydı. Takip süresi sonunda 10 hastada (% 38) taş olayı görülmedi ve tüm hastalarda hasta-yılı başına taş olayı 0.36'dı. Çalışmanın başlangıcında düşük eGFR'li dört hastanın eGFR'sinin takipte tedavi ile normale geldiği görüldü.

Sonuç: Sistinüri, düzgün kontrol altına alınmazsa önemli morbiditeye sahiptir. Tüm tedavilere rağmen sistinüride böbrek yetmezliği gelişebileceği akılda tutulmalı ve minimal invaziv seçenekler düşünülerek cerrahi tedavi planlanmalıdır.

Anahtar Sözcükler: Çocuk, Sistinüri, Ürolitiazis, Böbrek Taşı

INTRODUCTION

Cystinuria is an autosomal recessive disease that is characterized by elevated urinary excretion of dibasic amino acids (lysine, arginine, ornithine, and cystine) (1,2). Although urolithiasis is the most clinical manifestation of cystinuria, repeated stone formation in affected patients often causes considerable morbidity (3-5). In the general population, cystine stones account for 0.9 to 2% of all cases of urolithiasis (6). On the other hand in Turkey, there is a frequency of cystine stones between 7-17% of urinary stones (8). For the management of cystine stones, forced hydration, urinary alkalinization and the administration of sulfhydryl compounds have been recommended for the prevention of stone recurrence. However, the effectiveness of these treatments remain controversial, and surgery is frequently required to remove urinary stones (9-12). In addition, it is also accompanied by the risk of progressive renal impairment (13-15).

Our study aimed to assess the impact of medications and surgical interventions on renal function in cystinuric patients with cystine stones, which determine the prognosis in long term follow up.

MATERIAL and METHODS

The present study was carried out at the Ankara City Hospital (previously called Ankara Child Health Hematology-Oncology Training and Research Hospital) Pediatric Nephrology Department. The study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Medical Research Ethics Committee of Ankara Child Health Hematology-Oncology Training and Research Hospital (Protocol Number:2014-041).

A total of 26 cystinuria patients with cystine stones, aged between 3 months and 18 years, were retrospectively analyzed.

The diagnosis of cystinuria was made based on elevated urine dibasic amino acids and cystine levels according to normal values for age in urine amino acid analyzes. Normal urine cystine excretion was reported as 30 mg/L per day (0– 100 µmol/g creatinine) (3). The diagnosis of the cystine urolithiasis (stones) was based on an analysis of stone samples that obtained by spontaneous passage or surgery using the X-ray absorption method at the Institute of Mineral Inspection and Research Laboratory.

The blood urea nitrogen, serum levels of creatinine, sodium, potassium, chloride, calcium, uric acid, phosphorous, magnesium, arterial blood gas, urine analysis, parathyroid hormone and vitamin D were also recorded. Urine cultures were reviewed for bacteriological examination to check for urinary tract infections (UTIs).

Metabolic evaluations were performed for all patients. To define the metabolic abnormalities, the levels of calcium, oxalate, citrate, cystine, and uric acid were calculated by 24 hours urine analysis or by spot urine analysis. The absolute urine concentration of metabolic variables in the 24-hour urine or the mineral-to-creatinine ratio in spot urine was analyzed and compared with reference values (16).

Estimated glomerular filtration rates (eGFRs) were calculated using the bedside Schwartz creatinine-based formula (eGFR (mL/min/1.73 m^2)= k.height (cm)/plasma creatinine (mg/dl); where k is a constant = 0.413) at the beginning of the diagnosis and at the last visit (17).

For all patients, urinary ultrasonography (US) examinations were performed every 3-6 months.

Stone events were defined by the appearance of new stone or radiological evidence of stone growth.

All patients were advised to increase their fluid intake and to restrict their sodium intake (18). Trimethoprim-Sulfametoksazol (1-2 mg/kg/day) in a single dose was given to the patients with recurrent UTIs (16). Oral potassium citrate was prescribed for all patients at a dose of 1-2 mmol/kg per day in 3 divided doses to alkalinize the urine to a pH of 7 or 8 (18). Cystine-binding drugs were also given to all patients. Alpha-mercaptopropionylglycine at a dose of 10-20 mg/kg/day was our first drug of choice (18).

D-penicillamine treatment was started for two patients; however, due to the side effects of the drug (diarrhea, nephrotic syndrome), this treatment was replaced with alpha-mercaptopropionyl glycine (Thiola). We did not see any side effects with Thiola. Additionally, patients with other metabolic risk factors were treated according to their risk factors. Chlorothiazide (1-2 mg/kg day) was offered for hypercalciuria and pyridoxine (10 mg/kg/day) was also administered for hyperoxaluria (16).

Surgical management of cystine stones was performed by pediatric urology in our hospital depending on the size of the stone, its location and any signs of obstruction.

Data analysis and statistics

Data were evaluated using SPSS for Windows 11.5 (Chicago, Inc.) packet program. To compare the two groups, we used independent samples t-test if continuous variables have normal distributions, Mann-Whitney U test if continuous variables have not normal distributions. Chi-square test was used to evaluated categorical data. The relationship between variables was evaluated via Spearman Correlation analysis. The statistical boundary was accepted as 0.05.

RESULTS

Of the 26 patients with cystine stones, 23 were male (88.5%), and three were female (11.5%). The mean age at diagnosis was 45.2±45.5 months (range: 3 months-12 years), and the mean follow-up duration was 64.7 ±64.3 months (range: 7-204). On admission, five children (19%) were <1-year-old, fifteen (58%) were 1-5 years, and six (23%) were > 5 years.

Twelve children (46%) had positive family histories of urolithiasis. Consanguinity was also present in nine (35%) patients.

The most common presenting symptoms on admission were abdominal and flank pain (69%). The presenting symptoms and characteristics of the patients are shown in Table I. Sixteen (62%) children had also recurrent UTIs during their follow-up.

The mean serum creatinine levels at the first visit were 0.5±0.7 mg/dl (median:0.40 mg/dl). At the time of the patients' last outpatient visits, the mean serum creatinine level was 0.57±0.28 mg/dl (median: 0.56 mg/dl). A significant difference was detected between the first and the last visit creatinine levels (p=0.0008). Other serum biochemical values, parathyroid hormone levels, and vitamin D levels were within the normal ranges.

The mean first-visit eGFR and last-visit eGFR were 141.8±55.2 ml/min/1.73 m^2 (range: 10-244 ml/min) and 149.3±48.4 ml/min/1.73 m^2 (range: 61-266 ml/min), respectively, and these were not significantly different (p>0.05).

Four patients with eGFRs <90 ml/min/1.73 m^2 at the beginning of the study, used thiol drugs regularly, and the eGFR values of these patients increased to >90 ml/min/1.73 m^2 after the follow-up period.

The mean pre-treatment and last-visits' urinary pH levels were 5.5±0.63 (5-7) and 6.4±0.74 (5-8), respectively, and the urinary pH also significantly increased with treatment during the follow-up period (p<0.001).

Urinary evaluations revealed additional metabolic abnormalities in 10 patients. Only 16 (62%) children had isolated cystinuria.

Stone analyses were available for all children. One had both uric acid and cystine stones, and two had calcium oxalate stones in addition to cystine stones. The other children had only cystine stones.

Table I: Characteristics of patients with cystine stones.

Patients Characteristics (n=26)	
Male/Female	23/3
Age at diagnosis, months*	45.2±45.5 (3-144)
Follow-up period, months*	64.7±64.3 (7-204)
Age distribution	
<1 years	5 (19%)
1-5 years	15 (58%)
>5 years	6 (23%)
Positive family history	12 (46%)
Consangunity	9 (35%)
Symptoms of patients at first presentation	
Abdominal/flank pain	18 (69%)
Restlessness	16 (62%)
Urinary tract infection	16 (62%)
Hematuria	15 (58%)
Stone passage	7 (27%)
Enuresis	2 (8%)

**Mean ± SD (min-max)*

Table II: Correlation between the last-visit serum creatinine, eGFR levels and the number of surgical interventions.

		Correlations	
		Last-visit serum creatinine	Last-visit eGFR*
Number of surgical interventions	r	0.578	-0.169
	p	0.002	0.410
	N	26	26

**eGFR: estimated glomerular filtration rate.*

In 10 patients (38%), no stone events were observed during the follow-up period, and the stone event per patient-year was 0.36 for all patients.

There was no relation between family history of urolithiasis and the recurrence of stones in the patients (p=0.247). However, 75% of the patients with family histories of urolithiasis exhibited recurrence of cystine stones.

Moreover, there was no significant relation between UTI and stone size (p>0.05) or between UTI and the recurrence of stones (p=0.108). However, UTI was more common in patients with high numbers of stone recurrence.

An insignificant correlation was also observed between last visits' serum creatinine and number of stone recurrence (r=0.273, p=0.178)

The numbers of stone recurrences in patients with urinary pHs ≥6.5 were not significantly different (p>0.05). Although it is not significant, the number of stone recurrences in the patients with urinary pHs ≥ 6.5 was lower than that in the patients with pHs <6.5. In addition, the patients who used thiol drugs experienced a lower number of stone recurrence (r=0.491, p= 0.011)

Twenty-one patients received alpha-mercaptopropionylglycine as the first choice thiol-group drug. However, 3 patients did not receive thiol therapy despite being advised. Two separate patients also used it irregularly. D-penicillamine was given to two patients due to a lack of alpha-mercaptopropionylglycine, but during the follow-up period, the treatment was changed to alpha-mercaptopropionylglycine. The median duration of thiol drug usage was 27 months (minimum 1- maximum 201 months).

Prior to referral to our department, some of the patients had surgical interventions. Based on the available documents, of the 26 patients who were prescribed combined medical therapy, 2 patients only underwent ESWL, 4 had ESWL and surgery, and 17 patients underwent only surgical management that depended on the sizes and locations of the stones. Three patients had received neither ESWL nor surgery. Additionally, 9 patients required more than 1 surgical operation, and the patients underwent a total of 46 procedures and averaged 1.8 procedures per patient for 51 stone events.

There was a significant positive correlation between the last-visit serum creatinine level and the number of surgical interventions (p=0.002<0.05; r=0.578). On the other hand, there was no significant correlation between the last-visit eGFR and the number of surgical interventions (p=0.410>0.05; r=-0.169) (Table II). Although not statistically significant, eGFR values decrease as the total number of surgical interventions increases.

DISCUSSION

Approximately 6-10% of all urinary stone causes in children are cystine stones due to cystinuria (18). However, in Turkey, the frequency of cystine stone in Central Anatolia (within the area of our hospital) was reported as 3 to 12.5% (8). Therefore, cystinuria must be suspected in every pediatric stone patient with a family history of urinary stones. In cystine stones, regular follow-up and treatment are important due to the risk of high recurrence rates. On the other hand, it has also the risk of progressive renal failure (1-8,13-15,18,19).

Today, the management of cystinuria includes the elimination of stones and underlying metabolic disorders, prevention of the formation of new stones, control of UTIs, and also the preservation of renal function. However, the factors that directly cause cystine stone formation in childhood have not been clearly identified. Several studies have reported that high volume cystine excretion in the urine is a risk factor. It is known that cystine is insoluble at the physiological pH of urine. Thus, medical treatment should aim to reduce the cystine level and to increase the solubility of cystine in the urine. High levels of fluid intake, dietary sodium restriction, alkalinization of the urine with potassium citrate to maintain a urine pH>6.5 and the usage of thiol drugs are the main treatments (5,14-20).

In our study, a combination of potassium citrate and citric acid was used for alkalinization to maintain the urine pH>6.5. Moreover, we restricted the sodium intake of our patients and recommended increased fluid intake. At the end of the follow-up period, we found a significant increase in urinary pH levels compared to the pre-treatment pH levels (p<0.001).

Tekin et al. (21) reported that 66.7% of children with cystine stones who used alpha-mercaptopropionylglycine and potassium citrate had no stones at the end of the mean follow-up of 15 months. Furthermore, in another study, Izol et al. (22) demonstrated a 16.6% recurrence rate in patients who were receiving medical treatment and 100% in patients who did not receive any medical treatment. In our study, 20 of the 26 children received combined medical treatment regularly, and the mean follow-up period was 64.7±64.3 (range: 7-204) months. At the end of the follow-up period, 10 patients (38%) had normal urinary US with no stone formation. On the other hand, the stone events per patient-year in our study was 0.36, which is higher than reported in Japan (0.19) but lower than reported from the Cleveland Clinic (0.84 stone events per patient-year) (23,24). These differences may be attributed to the differences in the definitions of stone events, the subjective nature of stone growth assessment with the US, the efficiency of combined therapy, differences in diet, and differences in genetics. In addition, regular, long-term therapy is important for stone prevention. In the current study, we recommend thiol drugs for all patients during the follow-up period regardless of stone events, but three patients did not use thiol drugs.

Despite all of these combined therapies, many patients may require various surgical procedures, such as ESWL, percutaneous nephrolithotomy, retrograde intrarenal surgery, and rarely, open surgery, due to the high rate of stone recurrence, which is accompanied by a high risk of renal impairment (18,19,25,26). In a previous study, it was reported that male gender, high numbers of interventions, and histories of solitary kidneys are prognostic risk factors for renal insufficiency (21). Previous studies have also reported that serum creatinine levels are significantly higher in patients with cystine stones compared to those with calcium oxalate stones (22). In our study, 2 of the 26 patients underwent only ESWL, 4 underwent ESWL and surgery, and 17 patients underwent surgical treatment. Additionally, 9 patients required more than one surgical operation, and the patients underwent a total of 46 procedures and averaged 1.8 procedures/patient for 51 stone events, which is less than has been reported in some other studies (7.9 procedures/patient for 126 stone episodes) (26). Due to the risk of renal impairment, minimally invasive surgical interventions are preferable. In our study, some patients received some surgical procedures prior to referral to our hospital, and there was a significant positive correlation between the number of surgical interventions and the last-visit serum creatinine values. In contrast, there was no significant correlation between the last-visit eGFR and the number of surgical interventions ($p=0.410>0.05$; $r=-0.169$), eGFR values decrease as the total number of interventions increases. Whether this finding was coincidental or due to risk factors such as the high number of male patients and/or the high number of surgical interventions among our sample is unknown. It is difficult to resolve these questions due to the lack of genetic evaluations and the low number of female patients in this study.

CONCLUSION

It is important to remember metabolic diseases, such as cystinuria, as a cause of recurrent urolithiasis in children. Despite all treatments, it should be kept in mind that renal impairment may develop in cystinuria and surgical treatment should be planned by considering minimally invasive options.

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