Cystinuria in a group of children in Iraq

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Abstract

Background: Cystinuria is an autosomal recessive defect in reabsorptive transport of Cystine and dibasic amino acids. Increased urinary excretion of Cystine, the least soluble of all amino acids, results in formation of stones**.**

Objectives: we report our experience with management of cystinuria in a group of Iraqi children.

Patients and Methods: from 1999 to 2006, all children with cystinuria were evaluated, treated and followed in Al – Kadhimiya Teaching Hospital.

Results: Twenty three patients with cystinuria having calculi (16 males, 7 females) were treated. Their age ranged from 10 months to 18 years.

Associated hyperuricosuria was recorded in 30.5%, hypercalciuria in 13% and hyperoxaluria in 4.3%. Follow up period ranged from 1 – 88 months.

Nine patients were treated with increased oral fluids and alkalis only.

D–Penicillamine therapy was given to 13 patients. Side effect to penicillamine was noticed in 4 patients (22.2%). Captopril was given to 4 patients. Extracorporeal shock wave lithotripsy (ESWL) was performed in 8 patients, and 18 patients underwent open surgical procedures.

The stone free rate was 55.6% with fluids and alkali alone, 58.3% with D–Penicillamine, 0% with Captopril and 50% with ESWL.

Combined treatments were required in 45% of patients. Stone recurrence rate was 70%.

Conclusion: Oral fluids and alkali was most successful when used in patients with mild disease. D–Penicillamine and ESWL had nearly equal rate of successful results.

Keywords: cystinuria, chlidren, calculi, urolithiasis

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Introduction

Cystinuria is an autosomal recessive defect in reabsorptive transport of Cystine and dibasic amino acids: Ornithine, Arginie and Lysine from the luminal fluid of the renal proximal tubules and small intestine [1 – 10].

Increased urinary excretion of Cystine (the least soluble of all amino acids) results in Cystine crystallization and formation of stones [1 – 10].

Cystinuria is the cause of 1 – 2% of stones observed in adults and up to 10% of those occurring in children [1, 3, 4, 8].

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In 1966, Rosenberg et al, described three types of Cystinuria according to urinary phenotype: I, II, III [1 – 5, 8, 10].

A new classification of the disease by the International Cystinuria Consortium follows the chromosomal localization of the mutation with type an on chromosome 2, type B on chromosome 19 and type AB on both chromosomes [1, 4, 8].

The only phenotypic manifestation of Cystinuria is Cystine urolithiasis, begins in the first decades and often recurs throughout a patient's life time [1, 3, 4, 10]. Surgical intervention is often necessary, but the cornerstones of treatment is medical prevention of recurrent stone formation [1, 3, 4, 8, 10].

Aim of study

To report our experience with presentation, management, clinical

course and outcome of a group of Iraqi children with Cystine urolithiasis.

Patients and methods

This prospective study was conducted in the Pediatric Nephrology Clinic in Al - Kadhyimia Teaching Hospital in Baghdad between January 1999 and April 2006.

Twenty-three children with Cystinuria, were evaluated, treated and followed.

Clerking included recording age, gender, age of onset of symptoms, age of diagnosis of stone disease, clinical presentation, past medical and surgical history, recurrence and family history of stone disease.

Every child was tested for plasma urea, creatinine, sodium, potassium, calcium, phosphorous, uric acid and alkaline phosphatase level. Their urine was analyzed by microscopy and cultured.

Twenty four hour urinary determination of calcium, oxalate and uric acid was done to all children. They remained on their usual diet. In the morning, their first specimen of urine was discarded; urine was then collected for 24 hours. In young children who are not toilet trained, urine was collected by use of adhesive urine bags. For older children, collection was into container.

Hypercalciuria (HCa) was defined as urine Calcium excretion of > 4 mg/ Kg/ 24 hr. [6, 11, 12, 13]. Hyperoxaluria (HOx) was defined as urine Oxalate excretion of > 55 mg/ 1.73 m^2/ 24 hr [6, 12, 13]. Hyperuricosuria (HUr) was defined as Uric acid excretion of > 815 mg/ 1.73 m^2/ 24 [6, 12, 13]. Urine amino acid excretion was tested in all children using thin layer chromatography as well as Cyanide – Nitroprusside test [5, 14].

Stones, when available, were analyzed chemically.

Patients were diagnosed as having Cystinuria on the basis of one or more of the following criteria:

1. Cystine crystalluria: was observed in 2 patients (18.7%) on urinalysis [1, 4, 5, 8, 10, 12].

2. Positive Cyanide – Nitroprusside test in all patients. [1, 4, 5, 8, 9, 12, 15].

3. Detection of urinary excretion of amino acids Cystine, Ornithine, Arginine and Lysine by thin layer Chromatography in all patients [5, 10, 12, 14].

4. Cystine (pure or mixed) composition of calculi obtained from 10 patients by chemical analysis [1, 4, 5].

All stones were documented radiologically by Renal Ultrasonography (US) and Intravenous Pyelography (IVP). Voiding Cystourethrography (VCUG) was done when Vesicoureteric Reflux (VUR) was suspected.

Treatment Programs included:

1. Oral fluids and Alkali: All patients were instructed to maintain a fluid intake throughout day and night to ensure at least 1.2 L – 2 L / m^2 or 40 ml/ Kg/ day of urine daily. The urine should be kept very light in color approaching that of tap water making it a habit to observe this aspect with each voiding [16]. Adequate hydration was monitored on follow up visits every 1-2 months by checking the specific gravity achieving 1.010 [1].

2.Alkalinization of urine to a PH at about 7.5 throughout the day and night was accomplished with oral administration of alkali in the form of Potassium Citrate 60 – 80 Meq/ day or Sodium Bicarbonate 0.2 g/ Kg/ day in divided doses. Dose was adapted to urinary pH. Checking urine PH was done by the patients at home using urine strip and in laboratory on follow up visits. Moderate salt intake was

instructed to all patients, not to add salt to their diet [1, 3, 4, 8, 9, 10, 12]. Limit intake to 50 mmol/ day [3].

3. D– Penicillamine (DP). : Starting dose of 20 mg/ Kg/ day was increased gradually up to 40 mg/ Kg/ day given orally in 2 - 4 divided doses with half the dose given at bed time [1, 3, 4, 8, 12]. Most of the patients received 3 divided doses

4. Captopril: Given orally in a dose of 2 mg/ Kg/ day with observation of blood pressure [1, 3, 4]. The patients were given 2 divided doses.

5. Extracorporeal shock wave lithotripsy (ESWL): ESWL was performed using the Siemens Lithostar lithotripter. Youngest patient among our series was 12 month of age.

6. Open Surgical Procedures done with cooperation of urology surgeons.

Outcome of various treatment modalities were categorized as: stone free, no change, decreased size and increased stone size [5] .

Results

Total number of patients was 23. Males were 16, females were 7. Their age ranged from 10 months to 18 years (median = 46 months and mean of 69.7 ± 12.8 months). The age at onset of first symptom attributable to stone disease ranged from 2 to 132 months (median = 17 months and mean of 35.1 ± 7.9 months). Age at the time of diagnosis of Cystinuria ranged from 2 to 132 months (median = 17 months and mean of 38.6 ± 8 months). Sixteen patients were diagnosed as cystinuria at their initial clinical presentation. Majority of patients (78.3%) had the onset of stone disease before 5 years of age. Sixteen patients (69.6%) recalled a family history of stone disease, 12 of 16 (75%) had parental consanguinity. The clinical presentation is shown in table 1. Most patients presented with passing stones spontaneously (52.2%) and gross hematuria (47.8%). Four patients presented with failure to thrive (FTT), one of them had associated celiac disease, the 2nd had recurrent UTI, the 3rd catch up growth on follow up and he was stone free and the 4th was lost to follow. Associated culture proven Urinary Tract Infection (UTI) was present in 9 patients (39.1%), 3 of them were symptomatic. None had vesicoureteric reflux (VUR). No anatomical anomalies were detected on imaging studies.

Calculi were located in the left Kidney of 13 patients (56.6%), in right kidney of 5 patients (21.7%) and bilaterally in 4 (17.4%). One patient had vesical and left ureteric stones in addition to both kidneys (4.3%).

Staghorn calculi were seen in 4 patients (17.4%). It was bilateral in 2 of them; with recurrent UTI while it was unilateral in the other 2 with sterile urine. Stones were analyzed from 10 patients (43.5%). They were composed of Cystine in 4, mixed Cystine with Calcium Phosphate or Oxalate in 4, Cystine with Uric acid in 1 and mixed Cystine, Uric acid and Calcium Phosphate in 1, see table 2. In 4 out of 6 patients with mixed calculi there were associated metabolic disorders (66.6%). Overall associated HUr was recorded in 7 patients (30.4%), HCa in 3 (13%) and HOx in one (4.3%).

The length of follow up ranged from 1 to 88 months (median = 9 months and mean = 28.7 ± 6.6 months). No follow up information were available in 3 patients. Ten patients were observed for 3 years.

Nine patients were treated with increased oral fluids and alkali. Three of those 9 patients were stone free at beginning of this therapy. In 1, the stone

passed spontaneously and in 2, stones dissolved as a result of prior DP therapy. All 3 remained stone free with fluid and alkali therapy. Six patients had X–ray evidence of calculi when this therapy was initiated. Two of these patients became stone free. Stone size was decreased in one patient. In 2 patients stone size was not changed and in one patient, the stone was increased in size.

Stone free rate for this therapy was (55.6%), recorded in 5/9 patients.

See table 3. Two patients with unchanged stone size or continued growth were found to have associated HCa + HUr. It was noticed that patients responding to this therapy either as stone free or decreased stone size have a milder disease in term of single stone, small stone (less than 5 mm) and no recurrence. Length of follow up for the patients on fluid and alkali therapy ranged from 7 – 42 months (median = 12 months and mean of 18.4 ± 4.9 months)

Thirteen patients with radiologically proven calculi (two of those 13 had bilateral renal stones) received DP in addition to fluid and alkali. Three of them received DP twice after recurrence of stones. Therefore DP therapy was instituted in 18 occasions. The duration of DP therapy ranged from 2 to 54 months. One patient received DP for 11 years before being involved in this study. Two patients were lost to follow up. In 4 occasions (22.2%), treatments were stopped because patients developed side effects to DP.

Accordingly only 12 occasions of DP treatment on 7 patients were evaluated. In 7 of those 12 occasions (58.3%), stones dissolved. Two out of 12 stones were reduced in size. One stone was unchanged in size and 2 stones continued to grow (Table 2). Length of follow up the patients on DP therapy ranged from 7 – 63 months (median = 31.5 months and mean of 32.5 ± 7.4 months).

Two patients with increasing stone size had associated metabolic disorders.One patient had HUR, the other patient had HUR + HCa. Chemical analysis confirmed mixed Cystine with Calcium Phosphate stone. The patient with unchanged stone size was not regularly complying with medication.

Of the 7 patients evaluated for DP therapy, 3 were continued on DP because of recurrence. In the other 4 patients, DP was stopped after dissolution of their stones.

Recurrence of new stones was detected within 2 and 4 months after stopping DP in 2 of them. Side effects to DP were recorded in 4 patients. Two patients developed thrombocytopenia, one developed nephrotic Syndrome and one patient complained of severe epigastric pain. All symptoms disappeared upon withdrawal of the drug but reappeared upon its recommencement.

Four patients received Captopril. Response was evaluated after 6 months. In 2 patients, stones increased in size. In one patient stone size was unchanged. In one patient stone mass was reduced (Table 2).

Eight patients underwent renal ESWL. Four of them had ESWL on both kidneys. Therefore, 12 ESWL treatments were evaluated.

Stone free rate for renal ESWL was detected in 6 treatments (50%). Reduction in stone size or unchanged stone size was seen in 3 treatments (25%) for each (Table 2).

From 3 patients with unchanged stone size, 2 had concomitant Captopril therapy and one had Staghorn calculus with recurrent UTI. The Highest number

of ESWL treatments was 7 on a left kidney in a patient with recurrent bilateral calculi.

Three ESWL treatments were performed in each of 5 patients. One ESWL treatment was performed in each of 3 patients. Length of follow up of the patients on ESWL ranged from 4 – 80 months (median = 47 months and mean of 40.9 ± 8.7 months)

Twelve patients had a total of 18 open surgical removals of stones. Seven (38.9%) surgical procedures were performed in 5 patients before referral to Al–Kadhymia hospital. One of those 5 had 3 open surgeries on the left Kidney.

Thirteen (72.2%) operations were renal, 3 (16.7%) on the ureter and 2 (11.1%) on the Bladder. Fifteen surgeries were done before medical therapy while 3 were done after medical treatment.

From 20 patient's follow up data, 12 patients (45%) required combined treatments in which more than one treatment modality was used. Fourteen patients developed 27 episodes of recurrence of stone disease (70%), one of them had 4 episodes of recurrence, 4 had 3, 2 had 2 and 7 patients had one recurrence.

Table 1: Clinical presentation of 23 patients with cystinuria

Clinical presentation	*No. of patients*	*(%)*
Passing stones/ gravels	**12**	**52.2**
Gross hematuria	**11**	**47.8**
UTI	**9**	**39.1**
Abdominal Pain	**8**	**34.8**
Dysuria	**6**	**26.1**
Failure to thrive	**4**	**17.4**

*Patient may had more than one clinical presentation

Table 2: Stone chemical analysis of 10 patients

STONE COMPOSITION	No.
Pure Cystine	**4**
Cystine + Calcium Phosphate or Calcium Oxalate	**4**
Cystine + Uric acid	**1**
Cystine + Uric acid + Calcium Phosphate	**1**

Table 3: Treatment modalities and clinical outcome

Treatment	*No. of treatments*	*Stone free*	*Reduced in size*	*No change in size*	*Increased in size*
Fluid and Alkali	**9**	**5 (55.5%)**	**1 (11.1%)**	**2 (22.2%)**	**1 (11.1%)**
D Penicillamine	**12**	**7 (58.3%)**	**2 (16.7%)**	**1 (8.3%)**	**2 (16.7%)**
Captopril	**4**	**0 (0%)**	**1 (25%)**	**1 (25%)**	**2 (50%)**
ESWL	**12**	**6 (50%)**	**3 (25%)**	**3 (25%)**	**0 (0%)**

Discussion

The genetic transport defect in cystinuria exists from birth and stone formation begins in the first decades of life in a rate of 80% and continues life long. [3, 4, 9, 10] This was reflected in our study by early onset of stone disease among the studied group. Some data reported equal incidence between sex [1, 8], other studies reported higher rates among males [5, 17]. Males often have early appearance of stones, more severely affected and produce significantly more stones than females [1, 4, 8], these findings might lead to early presentation and diagnosis of the disease and will be reflected as higher rates in males.

High rate of parental consanguinity which is common in our community and family history of stone disease is obvious because of autosomal recessive inheritance pattern of the disease [1, 3, 4, 6, 7, 8, 12]. Dahlberg et al reported 50% of family history of stone disease among his series [5].

An interesting finding was the presentation of 4 patients with failure to thrive in our study. Andrwes was the first to suggest that cystinuric patients were shorter than normal, Colliss and associates also reported that the average height of 44 cystinuric patients was 2.5 cm less than that of the normal population, he postulated that patients with Cystinuria were at slight nutritional disadvantage as a result of urinary losses and defective gastrointestinal absorption of Lysine, an essential amino acid [5]. Al–Hermi et al described failure to thrive as the presenting feature in 1 of 3 cystinuria cases in Bahrain [18]. A recent epidemiological study from UK revealed that the median height and weight of children with renal stones on presentation was lower than average, claimed that those children often have feeding and growth problems [19]. Concurrent illness may also be contributing factors for reduced growth as we noticed in our study.

Similar to our results, associated UTI was recorded in one third of Cystinuric patients by several repots, as the presenting complaint or as a complication of stone disease [1, 3, 5, 6, 8]

Infection with urease splitting organisms represents a major reason for failure of medical therapy and the need for surgery to eliminate all fragments of the calculus in order to sterilize the urinary tract [6].

Staghorn calculi are well recognized radiological appearance with Cystinuria [1, 9, 10, 18]. The permanent excretion of excessive amount of Cystine is spontaneously associated with the relentless formation of stones which can have a staghorn development [3]. Most often, these stones now are treated with combination of percutaneous nephrolithotomy / ESWL / second look nephroscopy, termed "sandwich therapy " ,which precludes the need for renal open surgery [1, 3, 4, 18]. Nearly similar to our results, pure cystine stones were observed in 60 – 80% of cases [1, 4].

Sakhaee et al observed that HCa, HUr and/ or Hypocitraturia may accompany Cystinuria, thus contributing to stone formation [3] Avoidance of foods with a very high Methionine content; which is the precursor of Cystine, could lower urinary Cystine excretion, achieving one goal of treatment. However; most authors believe that such dietary restriction is not advisable for children [3, 4, 12]. Low salt diet to about 1 mmol / Kg / day was effective in reducing urinary Cystine concentration in children, however long term

compliance even with modest salt restriction is often poor[3, 4, 12]. Because high sodium intake increases cystine excretion, potassium citrate was preferred for most of the studied patients [1, 3, 8, 10].

A high fluid intake remains the most important factor for the reduction of urinary Cystine concentration which should be distributed throughout day and night [3, 4, 7, 10]. It was calculated that urine excretion of > 3 – 4 Liters/ day (1.2 – 2 liters/ M^2/ day or 40 ml/ Kg/ day in children) is necessary to prevent stone formation [1, 3, 9, 12]. Urine dilution alone is rarely sufficient and sustained alkalinization to PH of about 7.5 is often required to obtain effective Cystine solubilization [3, 4, 7, 10, 12]. The first stone dissolution by alkilinization of urine was reported in 1924, and alkilinization has been the mainstream treatment for over 50 years [9]. Alkaline urine can prevent precipitation of cystine calculi and even aid in dissolution [1]. Dent et al assessed the efficacy of large urine volume with alkali (Sodium or Potassium Bicarbonate) on Cystinurics. He reported that 12 of 18 stones of his series either dissolved or patients remained stone free [9]

In a study from Japan, in 3 cases out of 15 children with cystinuria, calculi disappeared by medical therapy alone [17].

We could not correlate our results with urine Cystine level; due to lack of laboratory resources. In Mayo clinic series; successful therapy was obtained in 10 out of 30 patients treated with oral fluid and alkali only [5].

For stone free patients; first line therapy is the conservative approach, is adequate for stone prevention [1, 3, 5]. This observation was highlighted in our study as 3 patients who did not have stones at onset of conservative therapy, continued to be stone free.

When conservative measures fail, the application of chelating agents that transform Cystine into a highly soluble Thiol–Cysteine mixed disulfide may be added. The most widely used drugs are DP and α – mercaptopropionyl – glycine or Tiopronin (TP), both drugs are equally effective [3, 4, 7 – 10, 12].

DP was introduced as a treatment for Cystinuria in 1963 [9]. Over the next few years, there were many small published series demonstrating reduction in Cystine excretion, stone dissolution and reduction in recurrence not controlled by oral fluids and alkalinization [9]. DP is best suited for stone prevention after surgical debulking of stone burden [1]. This observation was noticed in 4 occasions in our study. The same was observed in 3 out of 24 patients in Mayo clinic, where 10 patients had complete dissolution of calculi. Stone mass was reduced in 5, no change in stone size in 3 and stones continue to grow in another three [5]. Prevalence rate of adverse reactions to DP is approximately 20 – 50% in several studies [1, 3, 4, 5, 7 - 10]. Higher rate of side effect (85.7%) to DP was reported in a Japanese Study [17]. Coexisting metabolic disorders and presence of mixed calculi were emphasized as the most common reason for failure of DP therapy [3, 5] TP is preferred by most physicians in treatment of cystinuria, because of it's less side effects and can be used in patients who develop allergic reactions to DP [1, 3, 4, 8 – 10] Being unavailable in our country, TP was not used for the studied group.

Compared to the small series in this study, several studies failed to observe a significant effect of Captopril on Cystine stones formation [3, 9, 20].

Because of its low morbidity, ESWL can be offered as first line treatment for Cystine stones in children [1, 4].

Cystine stones often require urological intervention when they cause symptoms, obstruction, and increase in size [1, 3]. Although Cystine stones respond less to ESWL than Calcium stones, the stone free rate after ESWL is higher even for large ones in children than adults[4]. Because of their hardness and homogenous amino acid composition, most Cystine stones require multiple cessions to achieve acceptable stone free rates [1, 3]. This observation was also highlighted in this study. The response to ESWL is recorded in this study as the final result of completing treatments. Medical treatment was used in all patients underwent ESWL.

Stone free rate following ESWL was 43% in a Japanese study with an average of 5.9 sessions [17].

Open surgery should be considered for cases with complex staghorn calculi, difficult anatomy and simultaneous urological abnormalities [4]. As many patients will suffer recurrence of stones within a few years and need repeated urological intervention, minimally invasive procedures should be preferred to open surgery whenever possible [1, 3] . In a study from Japan, 17 lithotomies were performed in 13 out of 15 patients [17]

Treatment of patients with Cystinuria requires close co operation between the urologist and the nephrologists [1, 3, 4].

Regular medical treatment is mandatory because of the relentless tendency of cystine stones to recur despite improved urological techniques of stone removal [1, 3].

The main deficiency of this study is in the inability to quantitatively measure urine cystine, an important tool in the assessment of treatment efficiency. However it was believed that fellow up on stone formation rate provide a real picture of the clinical outcome.

In conclusion, oral fluids and alkali were most successful when used prophylactically in the stone free patients. D-Penicillamine and ESWL had nearly equal rate of successful results. Failure of treatment should alarm the possibility of coexisting metabolic disorders and UTI as a complicating problem. Combined treatments were frequently required in cystinuric children.

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