Nephropathic Cystinosis in Patients Attending Child Central Teaching Hospital

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ABSTRACT

Background: Cystinosis is a rare autosomal recessive lysosomal disorder characterized by the accumulation of the amino acid cystine in lysosomes of cells of different organs and tissues. It is a multi-systemic disease that can present with renal and extra-renal manifestations. Most cystinosis is the nephropathic infantile form, as indicated by its apparent and severe clinical manifestations, including renal and ocular symptoms.

Objectives: The important role of presenting symptoms and family history in the early diagnosis of cystinosis. In addition, to obtain an idea about the role of cysteamine in treatment of cystinosis.

Methods: In this retrospective, descriptive study, forty patients who were diagnosed as cases of cystinosis in nephrology consultation clinic in Child Central Teaching Hospital in Baghdad of Iraq, over a period of two years, from the 1st of January 2016 to the 31st of January 2018, were included in this study.

Results: The age of presentation of symptoms of renal tubular dysfunction in this study ranged (3 months - 10 years) with a mean age 1.6 year, 55% were females. History of consanguinity was positive in 32(80%) of patients parents. All patients (100%) presented with failure to thrive, polyuria and polydipsia. Regarding ocular complications that found in the patients, 32 (80%) had photophobia. Thirty-three patients used cysteamine therapy and only nine (22.5%) used cysteamine eye drops. Before use of cysteamine, thirty (90.9%) patients have elevated levels of serum creatinine and three (9.1%) patients have normal levels of s. creatinine while after use of cysteamine 15 (45.5%) patients have s. creatinine levels that is normal or near normal and 18 (54.5%) still has elevated levels of s. creatinine.

Conclusion: Cystinosis is a multi-systemic disease and without treatment it carries a great morbidity to affected individuals. Cysteamine is an effective therapy for this disease and should be started as early as possible to limit the rate of deterioration of renal function and should be used regularly even after renal transplant.

Keywords: Cystinosis, Extrarenal complications, Cysteamine therapy.

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Cystinosis is a systemic disease caused by a defect in the metabolism of cysteine that results in accumulation of cystine crystals in most of the major organs of the body, notably the kidneys, liver, eye and brain. Kidneys and eyes are especially vulnerable to damage; the muscles, thyroid, pancreas, and testes may also be affected(1). The prevalence of cystinosis is approximately 1:100,000 to 1: 200,000(2).

Cystinosis is classified into three clinical forms according to the age of onset and severity: 1. Infantile or nephropathic cystinosis, the most severe and frequent form, affecting about 95% of patients which results in poor growth and kidney complications in infants, known as renal Fanconi syndrome. Hypophosphatemic rickets, and poor growth at the age of 6-12 months(2). 2. Juvenile or late-onset nephropathic cystinosis is usually diagnosed later in childhood or during adolescence(2). 3. The ocular or adult form is characterized by isolated symptoms related to corneal cystine crystal depositions and is rarely diagnosed before adulthood(2).

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Cystinosis is transmitted as an autosomal recessive trait. The three clinical forms of cystinosis are caused by bi-allelic mutations in the CTNS gene (17p13.2) that encodes the lysosomal cystine transporter cystinosin[3].

Tissue accumulation of cystine remains the diagnostic hallmark of cystinosis and the diagnosis can be confirmed by performing the following tests: 1. Demonstration of corneal cystine crystals by the slit lamp exam. Cystine crystals in the cornea may not be apparent in the first months of life, but are always present by 18 months of age[2].

2. Measurement of leukocyte cystine levels (LCL); Measuring LCL requires dedicated laboratories; local reference values should be used. In general, levels are >2 nmol ½ cystine/mg protein in affected patients, whereas normal subjects have LCL <0.2 nmol ½ cystine/mg protein. This test not available in Iraq. 3. Genetic analysis of the CTNS gene[2] .

Prenatal diagnosis can be reliably performed on DNA samples isolated from chorionic villi or from amniotic fluid cells[4].

Symptomatic treatment of the renal Fanconi syndrome includes providing appropriate nutrition and substituting renal losses; these are crucial to allow satisfactory growth. Specific cystine-depleting treatment with cysteamine currently represents the mainstay of therapy, allowing depletion of lysosomal cystine in most tissues. It should be initiated as early as possible and continued lifelong. Although cysteamine does not cure the disease, it dramatically improves the overall prognosis[4].

Cysteamine (β-mercaptoethylamine) was first introduced as a possible therapeutic agent to treat cystinosis in 1976, and until now has been the only available treatment for the disease[5]. Cysteamine uses an unknown transporter to enter the lysosome and subsequently breaks the disulfide bond in cystine. This leads to formation of cysteine, which leaves the lysosome using the cystine transporter, and cysteine-cysteamine disulfide, which leaves the lysosome using the PQLC2 transporter[2,5].

Cysteamine remains the cornerstone of treatment for cystinosis and adequate administration of cysteamine significantly reduces the rate of progression towards end-stage renal disease, and postpones or even prevents the occurrence of extra-renal complications[6].

The pathognomonic and most frequently described ocular manifestation of cystinosis is deposition of cystine crystals in the conjunctiva and cornea. Corneal crystals typically appear as needle-shaped and highly reflective crystals by a slit lamp biomicroscopy[6]. Oral cysteamine has no effect on corneal cystine crystals. Patients need to be treated topically with cysteamine hydrochloride eye drops that dissolve crystals and alleviate symptoms at all ages[6].

Hemodialysis and peritoneal dialysis are temporary measures for end stage renal disease (ESRD) while patients are awaiting renal transplantation[7]. Renal transplantation is the treatment of choice of ESRD in cystinosis[8].

Methods

The data used in this study were collected using retrospective descriptive study, over a period of two years, from the 1st of January 2016 to the 31st of January 2018. The data of forty patients aged (3 months to 4 years) who were diagnosed as cystinosis in Child Central Teaching Hospital, treated and followed up in nephrology consultation clinic were included in this study.

The diagnosis of the disease was confirmed by finding cystine crystals in cornea through ophthalmological examination (slit lamp examination for corneal cystine crystals) that performed for all patients who were suspected to have cystinosis.

All patients except 7(18%) of them were treated with cysteamine and those 33(82%) patients were divided into two groups on the

basis of their history of cysteamine treatment. The two groups include patients with regular treatment and those with irregular treatment with cysteamine. This study gives an idea about the effect of cysteamine in preservation and improvement of renal function in patients with cystinosis. Patients also received symptomatic treatment that includes bicarbonate or citrate of potassium or sodium, indomethacin, calcium supplement, vitamin D supplement and dialysis for patients who reached end stage renal disease.

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 20.

Results

The age of presentation of symptoms of renal tubular dysfunction in this study ranged (3 months to 10 years) with a mean age 1.6 year. Eighteen (45%) were males, 22 (55%) were females. History of consanguinity of patients parents was positive in 32 (80%). Family history of affected siblings was positive in 11 (27.5%).

The majority of patients 25 (62.5%) have their residency in the western of Iraq, 13 (32%) from the middle and two (5%) from south of Iraq.

Regarding symptoms of presentation, all patients (100%) presented with failure to thrive, polyuria and polydipsia. Thirty (75%) had rickets, 6 (15%) had hypothyroidism. Patients with fair skin were 18 (45%) and patients not with fair hair and skin were 22 (55%), (Table 1).

Age of slit lamp examination ranged (6 months to 4 years) with a mean age 1.9 years. Regarding ocular complications that found in the patients, 32 (80%) had photophobia, 19 (47.5%) with cataract. Only 9 (22.5%) used cysteamine eye drops, (Table 2).

Out of the 40 patients, 33(82%) patients used cysteamine for the treatment of cystinosis. Cysteamine has an effect in improving renal function in those patients, by taking two readings for serum creatinine for each patient before and after using cysteamine for a year at least, it is revealed that there is improvement in the level of serum creatinine with the use of cysteamine. Before use of cysteamine, 30 (90.9%) out of 33 patients who used cysteamine have elevated levels of serum creatinine and 3 (9.1%) patients have normal levels of s. creatinine while after use of cysteamine 15 (45.5%) patients have s. creatinine levels that is normal or near normal and 18 (54.5%) still has elevated levels of s. creatinine (p value 0.002), (Table 3).

The greatest effect of cysteamine in preserving renal function appear in patients who used it regularly, those were 27 (67.5%), only 6 (40%) patients of them reached ESRD (end stage renal disease) while 21 (84%) patients not reached this stage. Patients with irregular use of cysteamine were 6 (15%), 3(20%) reached ESRD while 3 (12%) not reached this stage. Patients who did not used cysteamine were 7 (17.5%) patients, 6 (40%) patients of them reached ESRD and only 1 (4%) patient did not reached this stage (P value 0.007), (Table 4).

Table 1: Number and percentage of included cases, according to their main signs and symptoms, N = 40.

Characters	*Number*	*%*
Failure to thrive	40	100
Polyurea	40	100
Polydepsia	40	100
Rickets	30	75
Hypothyroidism	6	15
Fair hair and skin	*18*	*45*
Not fair hair and skin	*22*	*55*

Table 2: Age at slit lamp examination with number and percentage of ocular complications, N=40.

Age of Slit lamp Mean (Range)	**1.9 years (6 months to 4 years)**	
parameters	No.	%
Cataract	19	47.5
Photophobia	32	80
Use of Cysteamine eye drops	9	22.5

Table 3: Comparison of serum creatinine (s. creatinine) levels before and after treatment of patients with cysteamine, n=33.

Level	***S. Creatinine No. (%)***	
	Before treatment	After treatment
Normal	3 (9.1%)	15 (45.5%)
Elevated	30 (90.9%)	18 (54.5%)
Total	**33 (100%)**	**33 (100%)**
McNemar test, p-value= 0.002* (Significant at 0.05 level)		

Table 4: Relation between patients with end-stage renal disease and dialysis as well as cysteamine use, N=40.

Variables	***ESRD No. (%)***		***Total No. (%)***	***p-value***
	Yes	No		
Dialysis				
No	2 (13.3%)	25 (100%)	27 (67.5%)	<0.001*
Yes	13 (86.7%)	0 (0%)	13 (32.5%)	
Cysteamine bitartrate				
Not used	6 (40%)	1 (4%)	7 (17.5%)	0.007*
Irregular use	3 (20%)	3 (12%)	6 (15%)	
Regular use	6 (40%)	21 (84%)	27 (67.5%)	
Chi-square test, * significant at 0.05 level				

Discussion

Nephropathic cystinosis is an autosomal recessive disease that is usually found in societies where the rate of consanguineous marriage is high. In this study that included 40 patients with the disease, parents were consanguineous in 32 (80%) patients. This is similar to what is found in Egyptian study by Soliman NA, El-Baroudy R, Rizk A, et al[8] where the rate was also 80%, in a study in Iran by M. Mirdehghan[9] all patients were the result of consanguineous marriage.

Family history of other affected siblings were positive in 11 (27.5%), in Egyptian study[8], it was positive in (40%).

In this study 18(45%) patients were males and 22 (55%) were females, nearly the same results found in the Egyptian study[8], where 50% were males and 50% were females.

In this study the age of onset of symptoms ranged from (3 months-4 years) with a mean age 1.6 years and the first reported symptoms were those of renal tubular acidosis, all of patients in this study

(100%) presented with polyuria, polydipsia and failure to thrive. In the Egyptian study[8], the age of onset of symptoms ranged from (3 to 36 months) and this is nearly the same to what is found in this study, symptoms of renal tubular acidosis reported in 11 cases out of 16. Failure to thrive in Egyptian study[8] like this study present in all patients, the same was found by M. Mirdehghan[9] where the most frequent symptom of presentation was failure to thrive along with dehydration.

In this study rickets was founded in 30 (75%) patients and hypothyroidism was founded in 6 (15%) patients, in the Egyptian study[8], rickets was founded in 5 cases out of 16 patients and hypothyroidism was diagnosed in 3 patients. Rickets was diagnosed in all patients (10 patients) and hypothyroidism in two patient out of 10 patients by M. Mirdehghan.

The diagnosis of cystinosis was confirmed by finding corneal cystine deposits by slit lamp examination that performed for all patients, the age at which diagnosis confirmed by slit lamp examination ranged from (6 months - 4 years) with a mean age 1.9 years. In the Egyptian study the range of age for diagnosis by slit lamp was from (10 to 12 months), the age is older than what was founded in this study[8].

Regarding ocular complications in this study 32 (80%) patients had photophobia, 19 (47.5%) were diagnosed with cataract. In Egyptian study 8 (50%) had photophobia and 1 (6.25%) was diagnosed with cataract[8].

Only 9 (22.5%) of the patients in this study have been using cysteamine eye drops this can be due to the difficulty to obtain the drug and its expensive price and this can be the cause behind the high percentage of patients with ocular complications.

The use of oral cysteamine in the treatment of cystinosis had effect in improvement of renal function as obtained from the results of measurements of s. creatinine in patients in this study before and after the use of cysteamine. Before the use of cysteamine patients with normal values of s. creatinine were 3(9.1%) and patients with elevated values of s. creatinine were 30 (90.9%) while after using oral cysteamine in the treatment, patients with normal s. creatinine values became 15 (45.5%) and patients who still have elevated values of s. creatinine were 18 (54.5%) (p value 0.002, significant at 0.05 level) and these results agree with a study by Markello et al[10] who also found improvement in s. creatinine level with the use of cysteamine especially if drug use was regular. This also agree with a study by Van't Hoff WG et al[11] who found that the use of cysteamine significantly lower plasma creatinine concentrations in patients with cystinosis than a group of patients who did not receive cysteamine (P value 0.0001).

The regular use of cysteamine by most patients in this study can be the cause behind the role of cysteamine in lowering s. creatinine concentrations. This agrees with the results of a study in Spain by Ariceta et al[12] that found treatment with Cystagon (cysteamine) is effective in young patients and there is a good adherence to the drug in this age group. But this poses new challenges such as long-term compliance with a lifelong treatment, a difficult task in patients who take multiple medications and supplements for renal tubular acidosis, hypothyroidism as well as cystinosis.

In this study among patients who were using cysteamine regularly who were 27 patients, only 6 patients reached ESRD while 21 patients not reached this stage while among the 7 patients who did not used cysteamine, 6 patients reached ESRD and only one patient was not in this stage. So, cysteamine plays a role in preservation of renal function, this agree with the results found in a study by Brodin-Sartorius A[13] who reported that initiating cysteamine therapy before 5 years of age significantly decreased the incidence and delayed the onset of end stage renal disease and that life expectancy was significantly improved

in cysteamine-treated versus untreated patients.

In conclusion; Cystinosis is a multisystem disease that mainly present in societies where the percentage of consanguineous marriage is high and without treatment it carries a great morbidity to affected individuals. Cysteamine is an effective therapy for this disease, it limits the rate of deterioration of renal function and for optimal results to be obtained, this drug must be initiated early and used regularly.

Recommendations

1. Increase awareness of diagnosis and treatment of cystinosis.
2. Efforts to make the drug more available for all cystinotic patients due to its effect in attenuating renal and extra-renal complications.
3. Promote family and patients care by means of disease education programs.

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