

Natural History of Symptomatically Treated Children with Cystinosis

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ABSTRACT:

BACKGROUND:

Cystinosis is an autosomal recessive disorder of lysosomal transport of cystine . Nephropathic (infantile) cystinosis is the most common and the most severe clinical expression of the disease .

OBJECTIVE:

To highlight the natural history of symptomatically treated children with cystinosis

PATIENTS AND METHODS :

A retrospective study was done on cystinotic patients who were diagnosed and treated symptomatically in children welfare teaching hospital in Baghdad from period Jun 2002 –July 2011.

RESULTS:

Twenty nine patients ,19 (66%)males and 10(34%) females who were diagnosed as cystinosis and treated symptomatically were included in the study; their ages ranged between (0.6 -12) years median 4 years . the age of onset of symptoms of tubular dysfunction ranged from (0.3-3.5 yrs) median (1.1 yrs.), positive family history of cystinosis was found in 11(37.9 %) cases and parents were consanguineous in 25 (86.2%) families.

All patients presented with history of polyuria, polydypsia, anorexia, vomiting, constipation and failure to thrive.

Rickets was found in 22(75%)and photophobia was found in 19 (65.5%) patients.

Follow up data showed renal insufficiency in eighteen patients(62%) at a median age of 9(4-12) years ,hypothyroidism diagnosed in one patient(3.44%)at the age of 11 years , six (20.68%) patients died , three (10.3%)patients secondary to renal failure .

CONCLUSION AND RECOMMENDATIONS:

Cystinosis causes extensive morbidity and death in childhood and because of high rates of consanguineous marriages in our society ,

we encourage a high index of suspicion in infants presenting with fluid and electrolyte loss aiming at early diagnosis and treatment of cystinosis . leukocyte cystine levels is still needed to be available to confirm diagnosis in infants who have negative ocular examination .and to win in the fight against this terrible disease cysteamine treatment need to be available for these patients.

KEY WORDS : children , cystinosis , symptomatic treatment

INTRODUCTION:

Cystinosis is an autosomal recessive disorder of lysosomal transport of cystine ⁽¹⁾ associated with mutations in CTNS gene coding the lysosomal transport protein cystinosin.⁽²⁾ Nephropathic (infantile) cystinosis is the most common and the most severe clinical expression of the disease.⁽³⁾

Defective export of cystine from the lysosomes results in widespread accumulation of cystine crystals in various tissues and associated organ dysfunction.^(4,5,6)

Clinically, nephropathic cystinosis presents with infantile-onset renal tubular Fanconi syndrome and untreated cases progress to end stage renal disease (ESRD) later in the first decade.⁽⁷⁾

Cysteamine bitartrate (Cystagon®) has revolutionized the management and prognosis of nephropathic cystinosis. Cysteamine is now the treatment of choice for cystinosis throughout the world. This free thiol can deplete cystinotic cells of more than 90% of their cystine content. With effective cystine-depleting therapy, cystinosis was transformed from a progressive, fatal renal disease to a treatable chronic multisystemic disease, with life span increasing from about age ten years to at least age 50 years. Cysteamine therapy should be considered for all affected individuals, regardless of age and transplantation status.^(8,9)

Baghdad College of Medicine Children Welfare Teaching Hospital -Baghdad /Iraq.

PATIENTS AND METHOD :

A Retrospective study from period June 2002 – July 20011 in children welfare teaching hospital - medical city complex - Baghdad / Iraq

The data of 29 patients ,aged (1 month to 16 years) who were diagnosed as cystinosis in Child Welfare Teaching Hospital, treated symptomatically and followed up in nephrology consultation clinic were included in this study .

Clinical features ,history of consanguinity , family history of the disease ,lab results (blood picture and measurement of blood urea, creatinine, electrolytes, glucose, acid-base status, Free T4 and TSH.) were recorded from patients files.

ophthalmologic examination was conducted for all patients at the ophthalmology unit (This included funds examination and slit lamp examination for corneal cystine crystals)

diagnosis of cystinosis were suspected on the basis of presentation with proximal renal tubular acidosis and or hypophosphatemic rickets, or chronic kidney disease associated with previous history suggestive of renal Fanconi Syndrome particularly in families reporting death of siblings due to a similar condition.

The diagnosis was confirmed on findings of cystin crystals in cornea but leucocyte cystine assay which should be carried out as confirmatory diagnostic test is not available in Iraq .

The patients received symptomatic treatment aimed at correcting plasma disturbances from proximal tubule dysfunction , It consist of :-

1-Provision of large amounts of water and sufficient food

2-Bicarbonate (or citrate) of potassium and sodium, in 3-4 divided doses bicarbonate supplementation aimed at maintaining serum bicarbonate level around 20 mmol/l.

± potassium chloride or sodium in children who need more potassium or sodium than bicarbonate.

3-Active vitamin D supplement given in the form of 1& OH D3

At a dose of 0.5-1.5 µg/d to all patients

-Calcium supplement indicated for patients with renal insufficiency.

-Levothyroxin replacement needed in 1 patient age 11 years of age.

No patient in this study received oral cysteamine which is the drug of choice in cystinosis because it is not available in our country and those managed to take it from outside only four patients and doses were lower than recommended due to cost , they were not included in this study .

Statistical analysis included presentation of tables and data arranged in numbers and percentage while quantitative data were described using median and range .

RESULTS:

Twenty nine patients ,19 (66%)males and 10 (34%)females who were diagnosed as cystinosis and treated symptomatically were included in the study; their ages ranged between (0.6 -12) years ,median 4 years . the age of onset of symptoms of tubular dysfunction ranged from (0.3-3.5 yrs) , median (1.1 yrs.), positive family history of cystinosis was found in 11(37.9 %) cases and parents were consanguineous in 25 (86.2%) families. Table(1)

All 29 patients(100%) presented with history of polyuria, polydypsia, anorexia, vomiting, constipation, rickets and failure to thrive. Table (2) photophobia was found in 19 (65.5%) patients.

Follow up data showed: Table (3)

1-Renal involvement :twelve (41.3%) patients had Chronic renal insufficiency occurred at median 9(range 4-12) years of age. eight (27.5 %) of them were on conservative treatment only and 4(13.79 %) patients were on dialysis .

2- Ocular involvement

-Corneal infiltrates was noticed in 25(86.2%) patients ,age at diagnosis ranged (1.2-11years)

-Photophobia was noted in 18(62%) patients age ranged (3-12 years) ,median 7.5 years

3-Hypothyroidism diagnosed in one patient(3.44%) at the age of 11 years

Six (20.6%) patients died table (4), tow (6.89%) patients from severe gastroenteritis (one male and one female aged 0.8 and 1.9 years respectively), one male patient (3.4%) died from septicemia at 1.5 years and three patients (10.3 %) died from renal failure .

Table 1: Demographic Features of Cystinotic Patients

Features	(NO.)
Gender (F/M)	10/19
Age at diagnosis (years) Median (min-max)	4 (0.6-12 yrs.)
Age at symptoms onset ((years)) Median (min-max)	1.1 (0.3-3.5)
Consanguinity No.(%)	25(86.2)
Family history No.(%)	11(37.9)

M :F ratio 1.9:1

Table 2: Frequency of Presenting symptoms in patients with cystinosis

Presenting symptoms	No.of patients (100%)
polyuria, polydipsia (2-3 l/d)	29(100%)
anorexia ± vomitin	29(100%)
constipation	29(100%)
failure to thrive	29(100%)
Rickets	22(75%)

Table 3: Frequency of organs involvement in symptomatically treated with infantile cystinosis

Organ involved	Patient Age(years)	NO. (%)of affected patients
Chronic renal insufficiency	median 9 (range 4-12)	12 (41.3%)
Ocular (photophobia)	median 7.5 range (3-12)	18(62%)
Hypothyroidism	11 (year)	1(3.44)

Table 4 : Causes of death in patients with cystinosis (No.4)

Cause of death	Patient no. (%)
Acute gastroenteritis	2 (6.89%)
septicemia	1 (3.4%)
Uremia	3 (10.3 %)

DISCUSSION :

Cystinosis is an autosomal recessive inherited ,systemic disease . To high light problems of diagnose and treatment of infantile cystinosis a retrospective study was done in children welfare teaching hospital .

This study managed to diagnose infantile cystinosis in 29 children presented with tubular defect attending child welfare teaching hospital.

The diagnosis of patients in our study was dependent on finding of cystin crystal deposition in cornea by slit lamp examination .although Ocular examination can miss the deposition in some young aged patients and there will be delay in their diagnosis.

Diagnos of cystinosis is made by measurement of leucocyte cystine level; an assay which is not

available in our country. Demonstration of corneal cystine deposits by slit-lamp examination is diagnostic ,but It is expected that corneal deposits may still not be apparent in infants and should be interpreted with caution.^(10,11,12)

This study is first study on cystinosis in Iraq, in Egypt Cystinosis found to be significantly present given that in one study a two-year surveillance by one center diagnosed 16 cases while in USA 15 new cases are diagnosed annually⁽¹³⁾.

Because of nature of inheritance of the disease (autosomal recessive) and the high percentage of consanguineous marriage in our society .In this study 87% of the families had consanguineous marriage .We believe that more affected children are still undiagnosed and overlooked.

Clinical manifestations in young children usually reflect their pronounced tubular dysfunction and Fanconi syndrome.⁽¹⁰⁾

In our study all patients presented with manifestations reflecting their pronounced tubular dysfunction, the median age of symptoms presentation was at 1.1 years , which is consistent with infantile onset⁽¹⁴⁾

These symptoms are polyuria , polydipsia, growth failure, and rickets. A high frequency of vomiting, poor appetite, and feeding difficulties, combined with renal losses of nutrients, causes poor nutrition and failure to thrive^(1,15).

Treatment with replacement of renal losses resolves the rickets, tetany, acidosis, and laboratory abnormalities, and cystine-depleting therapy begun just after birth can attenuate the renal tubular Fanconi syndrome. However, renal tubular damage present at the time of diagnosis (i.e., approximately age one year) is irreversible⁽¹⁶⁾.

A high index of suspicion in infants presenting with fluid and electrolyte loss, renal tubular acidosis, rickets and growth retardation is encouraged ,aiming at early diagnosis .

Ocular changes include photophobia associated with corneal deposits, Various other extra-renal complications may occur including hypothyroidism, male hypogonadism, pancreatic endocrine and exocrine insufficiency, distal vacuolar myopathy, swallowing difficulties, decreased pulmonary function and neurological complications.^(17, 18,19,20,21,22,23,24,25,26)

In our study one patient presented with hypothyroidism at age of 11 years

Ocular manifestations photophobia secondary to corneal crystal accumulation found in 18(62%) patients at a median age 7.5 years.

Corneal crystals are initially asymptomatic, but photophobia can develop within the first few years of life⁽²⁷⁾.

In natural history of untreated nephropathic cystinosis , glomerular function gradually deteriorates, resulting in renal failure at approximately age ten years⁽²⁸⁾.

In our study 12 (41.3%) patients presented with CRI occurred at median 9(range 4-12) years of age. eight (27.5 %) of them were on conservative treatment and 4(13.79 %) patients were on dialysis , three patients (10.3 %) died from renal failure .

Cysteamine therapy is still not available in Iraq and it is cost make it difficult for parents to make it available for their children . Nevertheless, the cost of treatment is well justified considering the possibility of preventing the progression of renal and ocular problems as well as the occurrence of other complications.

CONCLUSION AND RECOMMENDATIONS:

Cystinosis causes extensive morbidity and death in childhood and because of high rates of consanguineous marriages in our society ,

we encourage a high index of suspicion in infants presenting with fluid and electrolyte loss aiming at early diagnosis and treatment of cystinosis . leukocyte cystine levels is still needed to be available to confirm diagnosis in infants who have negative ocular examination ,to win in the fight against this terrible disease cysteamine need to be available for these patients.

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