Characteristics and complications of childhood nephropathic cystinosis in Al-Fallujah City: a case series

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Abstract
Cystinosis is a rare inherited pediatric health problem. The most severe form of the disease "infantile or nephropathic cystinosis" can lead to serious complications including end-stage renal failure and death. The complications may be prevented with early diagnosis and proper treatment. The objective of the study was to estimate the frequency of nephropathic cystinosis pediatric cases in Al-Fallujah City during year 2013. The primary outcome of study was Nephropathic Cystinosis. The distribution of the characteristics was presented in number and percentages. The continuous variables were presented as mean and standard deviation (SD) and range. The distribution of the cases was assessed among different categorical groups including age, gender, residency and age at onset of diagnosis.

Thirty children were diagnosed with nephropathic cystinosis. Mean age of the cases was 4.6 Standard Deviation (2.9) (range 9m-15yr). 18 (60%) females were affected versus 12 (40%) males. Of the 30 cases, 29 (96.7%) were below eight years old. Most of the cases were living in Al-Fallujah city and surrounding villages (n=27, 90%). All of them had polyuria, polydipsia and growth retardation. Nephropathic Cystinosis patients are recognized in Al-Fallujah City and have a large impact on the children and their families. Infant with polyuria, polydipsia, growth retardation and rickets should be evaluated for the possibility of Cystinosis. Lack of medical equipments and medications in the local hospital are adversely affecting the proper management.

Keywords: Cystinosis, Cysteamine, Al-Fallujah.

Introduction

Cystinosis is a rare pediatric health problem and can affect 1: 100,000 to 200,000 live births.[8] Cystinosis is a systemic disease caused by a defect in the metabolism of cysteine and leads to accumulation of cystine crystals in the major organs of the body including kidney, liver, eye and brain. There are three different types of cystinosis: (i) Nephropathic cystinosis; (ii) Intermediate cystinosis; and (iii) Non-nephropathic or ocular cystinosis. The most severe form of the disease, "infantile or nephropathic cystinosis", develops during the first two years of life manifested with severe tubular dysfunction and growth failure. If the disease is not diagnosed and treated early, it will progress to end-stage renal failure by the end of their first decade and death.[8]

Cystinosis is an inherited disorder that belongs to lysosomal storage disease disorders.[4] CTNS gene mutations are responsible for codes for cystinosin, which is the lysosomal membrane-specific protein transporter for cystine and leads to the development of the disease. Metabolism of cystine, inside the cells, needs to cross the cell membrane. After transformation of endocytosed protein to cystine, within lysosomes, it will be transported to the cytosol. If there is abnormality in this carrier protein, cystine will be accumulated in the lysosomes. As cystine is highly insoluble and when its level increases in tissue lysosomes, its solubility is immediately exceeded and crystalline precipitates are developed in most of organs and tissues.[9]

Furthermore, elevated intracellular cystine will disturbs metabolism of cellular oxidative and glutathione status[5] leading to disturb metabolism of mitochondrial energy, autophagy and apoptosis.[6] However, the disease progression is correlated to the accumulation of crystals in the tissues. Therefore, the mechanisms of tissue damage are not fully understood. Cysteamine is the drug of choice in treatment of cystinosis, which decreases the accumulation intralysosomal cystine.[10]

Infants affected by nephropathic cystinosis initially exhibit poor growth and abnormal kidney function, referred as "renal Fanconi syndrome". The abnormal kidney function leads to the loss of fluids, salts minerals and other nutrients. The loss of nutrients will impair growth and will result in bones deformity "hypophosphatemic rickets", especially in the lower limbs. Also, the nutrient imbalances result in polyuria, thirst, dehydration and acidosis.[2]

At two years of age, cystine crystals may start to precipitate in the cornea leading to increased eye sensitivity to light "photophobia". Untreated children with cystinosis are likely to develop complete kidney failure by ten years of age. With progress of the illness, the children might suffer from other serious complications such as muscle function impairment, blindness, swallowing difficulties, impaired sweating, loss of hair and skin pigmentation, thyroid dysfunction, diabetes and nervous system complications.[3]

Material and Methods

Study design, data source and population: This was a case series study design. The deidentified data were collected

from parents attending a pediatric private clinic practice from 1st January to 31st December 2013.

Study data: The demographic characteristics and potential risk factors included age, gender, residency, age at onset of diagnosis, consanguinity of parents, family history of Cystinosis, death of relatives from similar disorder, regular doctor visits and check-up, tolerance to management and instructions, growth parameter, renal function, potential complications and interventions including conservative and surgical interventions such as renal transplantation. Patients' investigations, including blood gas analysis (BGA), blood Urea-Nitrogen (BUN) and complete blood count, were collected from blood test reports.

The accompanied parents were asked to participate in the study by filling a standard questionnaire form and provide formal consent. The questionnaire was assigned to include:

1. Age.
2. Gender.
3. Residence.
4. Age at onset diagnosis.
5. Growth parameters (height and weight).
6. Was the blood urea and serum creatinine elevated or not at time of study?
7. Was the patient on regular and continuous treatment including cysteamine?
8. Was the patient on regular checking of blood gas analysis (BGA) and other investigations or not?
9. Is there any family history of Cystinosis?
10. Any death in family from similar disorder?
11. Consanguinity of the parents.
12. Clinical presentations in details.
13. Interventions including renal transplantation in advanced cases.

Outcome: The primary outcome was Nephropathic Cystinosis. The diagnosis of cystinosis is based on clinical manifestations, development of corneal cystine crystals (reported by ophthalmologist) and abnormal blood test report including BGA and renal function test.[8]

Statistical analysis: The distribution of the characteristics was presented in number and percentages. The continuous variables, including age, age at onset of diagnosis and Body Mass Index (BMI) were presented as mean and standard deviation (SD) and range. The distribution of the cases was assessed among different categorical groups including:

- Age: <2yr, 2-4yr, 4-6yr, 6-8yr, >8yr;
- Gender: male and female;
- Residential area: Al-Fallujah city, Al-Nassaf village, Al Saqlawyah city, Al Garmah City and Others;
- Age at onset of diagnosis: <6months, 6-12months, 12-18months, >18months

Results

Thirty children were diagnosed with nephropathic cystinosis. Mean age of the cases was 4.6 years (SD=2.9) (range 9m-15yr), mean age at onset of diagnosis 12 months (SD=6) [range 2m-24m] and BMI mean was 17.5 Kg/m^2 (SD=5.8) [range 13-40]. Female are more affected than male (n=18, 60% versus n=12, 40% respectively, figure 1). The demographic characteristics and the distribution of the potential risk factors are summarized in table 1.

Table 1
Demographic characteristics and distribution of potential risk factors and complications of Cystinosis in children

Factor	N (%)
Sociodemographic factors	
Gender	
male	12 (40%)
female	18 (60%)
Residential area	
Al-Fallujah	27 (90%)
Others	3 (10%)
Age at onset of diagnosis	
≤12 months	19 (63%)
>12 months	11 (37%)
Consanguineous parents	
Yes	27 (90%)
No	3 (10%)
Clinical factors	
Polyuria & polydipsia	
yes	30 (100%)
no	0
Growth Retardation	
yes	30 (100%)
no	0
Anemia	
yes	27 (90%)
no	3 (10%)
Dental problems	
yes	26 (86.7%)
no	4 (13.3%)
Rickets	
yes	23 (76.7%)
no	7 (23.3%)
Photophobia	
yes	21 (70 %)
no	9 (30%)
Alopecia	
yes	13 (43.3%)
no	17 (56.7%)
Interventions	
Regular therapy	
yes	14 (46.7%)
no	16 (53.3%)
Renal transplantation	
yes	2 (6.7%)
no	28 (93.3%)

Of the 30 cases, 29 (96.7%) were below eight years old (table 2). Most of the cases were living in Al-Fallujah city and surrounding villages (n=27, 90%, table 3). The distribution of height and weight were demonstrated in figure 2. All patients fell below the third percentile as shown in figure 2. Twenty-seven patients (90 %) were product of consanguineous parents (figure 3). Half of patients (n=15, 50%) had family history of cystinosis or death of relative from similar disorder.

The distribution of age at onset of diagnosis was summarized in table 4. More than one third (n=12, 40%) are between 6 months and 12 months of age at onset of diagnosis.

Table 2
Distribution of the cystinosis among age groups (n=30 patients)

Age in years	N (%)
<2 yr	5 (16.7%)
2- 4 yr	12 (40%)
4-6 yr	6 (20%)
6-8 yr	6 (20%)
>8 yr	1 (3.3%)

Table 3
Geographical distribution of the cystinosis (n=30 patients)

Residential area	N (%)
Al-Fallujah City	11 (3.7%)
Al-Nassaf village	10 (33.3%)
Al Saqlawyah city	14 (3.3%)
Al Garmah City	2 (6.7%)
Others	3 (10%)

Table 4
Shows distributions of the age at the onset of diagnosis (n=30)

Age group	N (%)
<6 months	7 (23.3%)
6m – 12m	12 (40%)
12m – 18m	7 (23.3%)
>18m	4 (13.4%)

Table 5
Distribution of clinical factors and complications of cystinosis in children

Presentations	N (%)
Polyuria and polydipsia	30 (100%)
Growth Retardation	30 (100%)
Anemia	27 (90%)
Dental problems	26 (86.7%)
Rickets	23 (76.7%)
Photophobia	21 (70 %)
Alopecia	13 (43.3%)

All of them had polyuria, polydipsia and growth retardation. Other manifestations and complications were: anemia (n=27, 90%), dental problems (n=26, 86.7%), rickets (n=23, 76.7%), photophobia (n=21, 70%) and alopecia (n=13, 43.3%) (table 5). Nine patients (30%) had elevated Blood Urea-Nitrogen (BUN) and serum creatinine (figure 4).

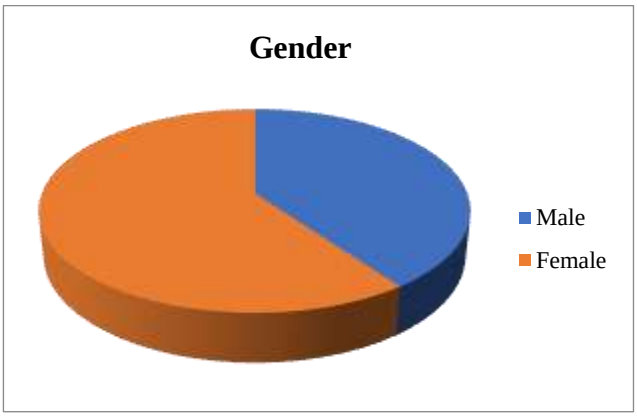

Figure 1: Distribution of gender in Cystinosis (Female 60%, Male 40%); Female : Male ratio 3:2

Figure 5 shows that five (16.7%) patients were performed regular checking of Blood Gas Analysis (BGA) while 25 patients (83.3%) were not. Fourteen patients (46.7 %) received regular Cysteagon and other therapy while more than half of the patients (n=16, 53.3%) did not receive it due to hard financial situations. Only two patients (6.7%) had undergone renal transplantation.

Discussion

Main findings: This study involves 30 patients of nephropathic cystinosis being diagnosed according to clinical and laboratorial investigations. The gender of patients was predominantly females who were 18 (60%) while males was 12 (40%). Majority of the patients were below 8 years (96.7%). The numbers of the patients who were on regular conservative therapy were 14 (46.7%) and only two (6.7%) patients had undergone renal transplantations.

Strength and limitations: The main limitation of our study is short study period that allowed obtaining only a small sample since the disorder is rare and study was limited for outpatient private clinic. Unfortunately, the collection of data was stopped for situations beyond control when the war started and people forced to leave the city. Other limitations are lack of facilities and proper health services in the local hospitals that limit the patient's follow up; lack of cooperation of some families limits the follow up and proper managements.

Interpretations: Out of 15 children identified with infantile cystinosis in a study conducted in Egypt, ten were reported to have consanguineous parents[11] which is nearly similar to our study estimates. Other study reported the mean age of the 33 patients with cystinosis was 52.7 months which is

similar to our results.[12] Five patients developed end-stage renal disease and mean age of deaths is 24.3 months. In Oman, a 7-month old, infant which is also a product of first-degree consanguineous parents, presented with similar manifestations was reported in our patients in the same age group.[1]

In a study including ten cases of nephropathic cystinosis (4 males and 6 females), the authors reported the mean age of 12 months (range 5-20 months) which is lower than our study. This might be due to the study criteria to include patients in the first two years of life. Two patients reported hypothyroidism. The study reported four deaths (3 due to metabolic disturbance and one from end-stage renal failure).[7]

In the clinical practice, three different types of cystinosis were defined: nephropathic cystinosis, intermediate cystinosis and non-nephropathic or ocular cystinosis. This study is limited to a nephropathic type of cystinosis which is the most serious type that is affecting the infants since early life causing a lot of disabilities and complications if it is not properly managed.

As the disease develops during early child hood period, early diagnosis and proper management may render the disease to be non-fatal. Our study results estimated that only seven (23.3%) patients were diagnosed during the first six months. This might be belonging to the unawareness of the families about this problem, lack of the experience of the general practitioner (GP) in identifying the children at risk of developing the illness and shortage of the healthcare services and equipments in the villages.

Our study estimates support that the disease is an inheritant disorder. The number of the patients with positive consanguinity parents were 27 (90%) while only three patients were not, which may be explained by fresh mutations. Cystinosis is a life-threatening disorder so that 15 (50%) are having positive family history of death due to the same disease.

The study also reported on the clinical presentations of the patients which is shown in table 5 that shows all patients were complaining from the most common clinical factors reported worldwide including polyuria, polydipsia and growth retardation.[8] Other presentations were anemia (90%), Rickets (76.7%) due to Fanconi syndrome and hypophosphatemia,[8] dental problems (86.7%) due to the same cause of rickets.[8] Photophobia was reported in 21 patients (70%) due to cystine crystals in cornea and in-proper Cysteagon eye drop use. Alopecia was reported in 13 patients (43.3%) which might be due to the chronicity of the disease, anemia and growth retardation.[8] Other common symptoms like nausea, vomiting, constipations and craving for salty and acidic food were not included in the questionnaire.

Nine patients (30%) reported elevated BUN and serum creatinine which are attributed to many factors including the pathophysiology of disease, delay diagnosis, improper management, poverty, in addition to the difficulties in accessing the healthcare services and shortage of medications in the governmental health sectors. Other important issue is the absence of facilities for blood gases analysis in the local hospitals leading to irregular check-up of BGA by the majority of patients (n=25, 83.3%) which is certainly affecting the success of the management.

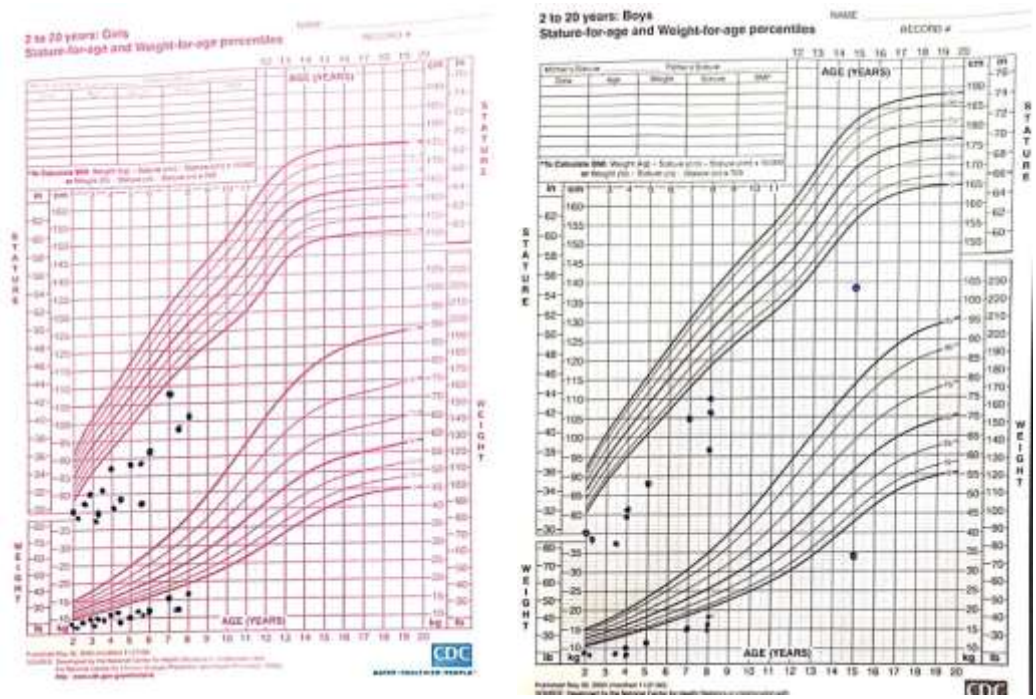

Figure 2: Growth charts show the distribution of height and weight of cystinosis in children

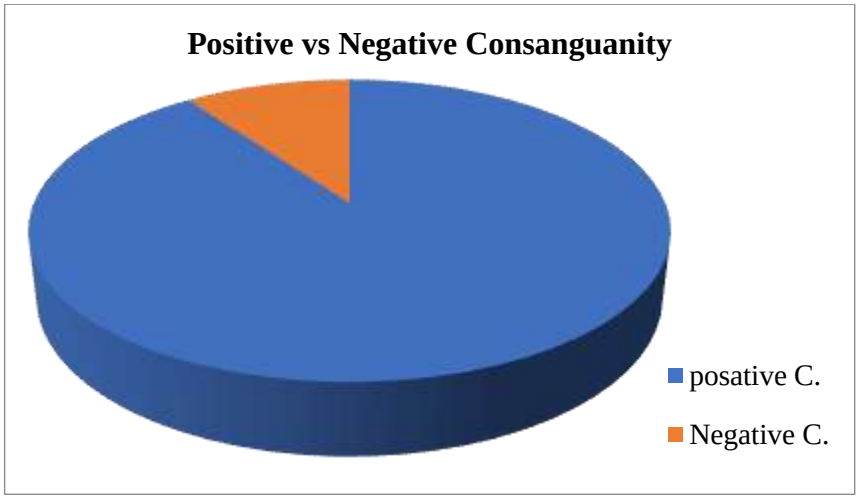

Figure 3: Positive versus Negative consanguineous parents in childhood cystinosis

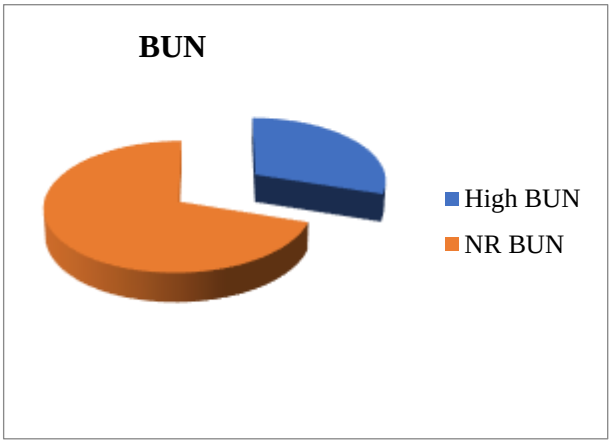

Figure 4: The distribution of high BUN in cystinosis (n=9, 30%)

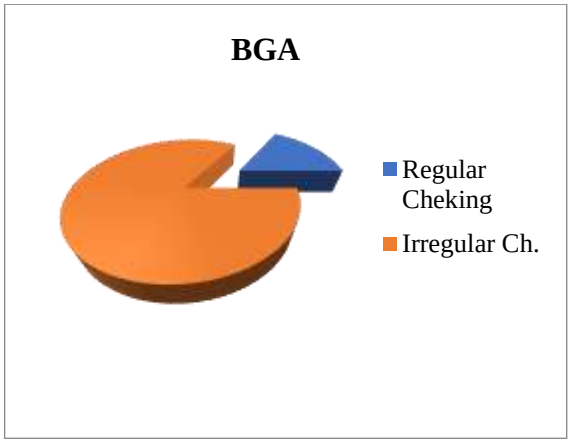

Figure 5: Number and parentage of patients performed regular checking of BGA (n=5, 16.7%)

Half of patients (n=14, 46.7%) received regular therapy and this is greatly related to the illiteracy and poverty. Only two (6.7%) patients underwent renal transplantations which is very expensive and the majority of the patients could not afford the expenses.

Study highlighted the requirement of further development and researches to identify the risk factors of the disease. Early prediction and prognostic tools, including developing national guidelines or prediction and prognostic models, can be helpful in the developing preventive and prognostic strategies to prevent complications and improve outcomes.

The study results support the need to increase the awareness of the health professionals and the parents about the importance of the early diagnosis and proper management in preventing the diseases complications and render the disease to be non-fatal illness. Furthermore, the provision of medical services and equipments and accessible health services will greatly contribute in better prognosis.

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