Gastrointestinal Manifestations of Nephropathic Cystinosis in Children

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Introduction. Cystinosis is an autosomal recessive disorder which is characterized by both renal and extrarenal symptoms. Gastrointestinal dysfunction has been reported in adolescent with cystinosis, and it is rarely considered in the infants. The present case series reviewed gastrointestinal manifestations of these patients.
Materials and Methods. Gastrointestinal signs and symptoms of 23 children aged 5.99 ± 0.50 years (range, 1.0 to 12.5 years) on average with cystinosis, admitted to our department of nephrology between 1996 and 2005, were retrospectively reviewed. The inclusion criteria were the presence of the crystals of cystine in bone marrow aspiration and corneal deposition detected by slit lamp examination.
Results. Gastrointestinal signs and symptoms were as follows: vomiting in 16 patients (69.6%), hepatomegaly in 8 (34.8%), diarrhea in 6 (26.1%), splenomegaly in 5 (21.7%), constipation in 4 (17.4%), anorexia in 4 (17.4%), abdominal pain in 3 (13.0%), nausea in 2 (8.7%), and ascites in 2 (8.7%). Height below the 3rd percentile in was seen in 16 patients (69.6%) and weight below the 3rd percentile, in 17 (73.9%). Fifteen patients (65.2%) had both low weight and low height. Esophagogastroduodenoscopy had been performed in 6 cases and chronic inactive gastritis with *H pylori* infection was detected in 2 patients (8.7%).
Conclusions. Our study revealed a wide spectrum of gastrointestinal disturbances in young patients with cystinosis. Such findings should lead to greater awareness of the presence of gastrointestinal dysfunction in these children, encourage prompt gastrointestinal evaluation, and encourage treatment of more severely affected patients.

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INTRODUCTION

Cystinosis is an autosomal recessive disorder characterized by both renal and extrarenal symptoms due to the intracellular accumulation of cystine in different tissues and organs. Gastrointestinal dysfunction, one of the extrarenal manifestations, is rarely considered in the infants with cystinosis.[1] There are very few articles on gastrointestinal problems in young children with cystinosis.[2-4] Gastrointestinal dysfunction in adolescent has been reported as a result of cystine crystal deposition in smooth muscles leading to oropharyngeal dysfunction.[1] Vomiting, changing bowel habits, abdominal pain, and swallowing dysfunction are the most frequently reported complains,[2,5] while noncirrhotic portal hypertension and cholestatic liver disease are reported as case reports.[3,6] Both cysteamine side effects and cystine deposit are reported as the etiology of these abnormalities.[1] In this study, we sought to find the frequency of gastrointestinal problems in pediatric nephropathic cystinosis.

MATERIALS AND METHODS

The clinical and laboratory data of 23 children with a diagnosis of cystinosis were reviewed

retrospectively. The patients were selected from among children admitted to the department of nephrology at Ali-Asghar Children Hospital, in Tehran, Iran, between March 1996 and February 2005. In this descriptive study, the principles outlined in the Declaration of Helsinki were followed. The inclusion criteria were the presence of the crystals of cystine in bone marrow aspiration and detection of corneal deposition by sit lamp examination by an expert ophthalmologist. Demographic variables including age, sex, height, and body weight were obtained from the hospital records. Gastrointestinal signs and symptoms including nausea, vomiting, diarrhea, hepatosplenomegaly, ascites, and failure to thrive were also extracted.

Hepatomegaly was defined as the palpation of the edge of the liver 2 cm below the costal margin or a liver span greater than the expected span in the right midclavicular line on percussion for age and sex, confirmed by ultrasonography.[7,8] Splenomegaly was considered in the case of palpation of the spleen below the costal margin, confirmed by ultrasonography.[8] Ascites was defined as detection of protuberant abdomen with bulging flanks, positive shifting dullness, and fluid wave.[8] Failure to thrive was referred to growth (weight and height) below the third percentile of age and sex. Anorexia was defined as poor appetite and no desire to have meals reported by the parents.[9]

Laboratory data including complete blood count; serum levels of urea, creatinine, and electrolytes; and liver function tests including alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, prothrombin time, partial thromboplastin time, total and direct bilirubin, serum albumin, and total protein were collected. Glomerular filtration rate (GFR) was calculated using the Schwartz formula and a GFR less than 15 mL/min was considered as end-stage renal disease.

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Quantitative variables were presented by central indexes (mean and standard deviation of mean) and qualitative variables were presented by frequency tables.

RESULTS

Demographic Characteristics

Twenty-three children (8 boys and 15 girls) with a mean age of 5.99 ± 0.50 years (range, 1.0 to 12.5 years) were included. Seventeen patients (73.9%) were children of parents with consanguineous marriage. Their mean body weight was 11.4 ± 4.7 kg and their mean height was 82.68 ± 19.43 cm.

Presentation

The most frequent sign of presentation was poor weight and height gain observed in 18 children (78.3%). Polyuria and polydipsia were detected in 10 patients (43.5%), and dehydration in 2 (8.7%).

Gastrointestinal Manifestations

Gastrointestinal signs and symptoms were as follows: vomiting in 16 patients (69.6%), hepatomegaly in 8 (34.8%), diarrhea in 6 (26.1%), splenomegaly in 5 (21.7%), constipation in 4 (17.4%), anorexia in 4 (17.4%), abdominal pain in 3 (13.0%), nausea in 2 (8.7%), and ascites in 2 (8.7%). Height below the 3rd percentile in was seen in 16 patients (69.6%) and weight below the 3rd percentile, in 17 (73.9%). Fifteen patients (65.2%) had both low weight and low height. Esophagogastroduodenoscopy had been performed in 6 cases and chronic inactive gastritis with *H pylori* infection was detected in 2 patients (8.7%). Table 1 shows the distribution of gastrointestinal symptoms and signs stratified by the estimated GFR. Only 2 children had received H2 receptor blockers. Two patients had been treated with metronidazole, omeprazole, and amoxicillin for eradication of *H pylori*.

Laboratory Studies and Diagnoses

All of the patients suffered from renal tubular acidosis. Seventeen patients (73.9%) had chronic kidney failure, 18 (82%) had hyponatremia, and 8 (34.8%) had hypokalemia. Two patients (8.7%) had developmental delay. Results of liver function tests were available in 7 patients, 1 of whom had a prolonged prothrombin time. Hypoalbuminemia was detected in 3 patients. Results of laboratory studies are shown in Table 2.

Outcome

After a mean follow-up of 5.60 ± 3.43 years, 7 patients (30.4%) had functional native kidneys, 5 (21.7%) had been transplanted, 9 (39.1%) were on long-term dialysis (3 on hemodialysis and 6 on peritoneal dialysis), and 2 (8.7%) had died.

Table 1. Frequency of Gastrointestinal Manifestations in Children With Cystinosis Stratified by Glomerular Filtration Rate

Manifestation	Glomerular Filtration Rate		Odds Ratio	95% Confidence Interval
	≤ 15	> 15		
Diarrhea	5 (29.4)	1 (16.7)	4.44	0.40 to 46.50
Constipation	2 (11.8)	2 (33.3)	0.58	0.06 to 5.10
Vomiting	10 (58.8)	6 (100)	1.25	0.20 to 7.60
Abdominal pain	3 (17.6)	0		
Nausea	2 (11.8)	0		
Abdominal distention	4 (23.5)	3 (50.0)	0.80	0.10 to 4.80
Dysphagea	0	1 (16.7)	2.75	1.58 to 4.78
Anorexia	2 (11.8)	2 (33.3)	0.58	0.06 to 5.00
Hepatomegaly	5 (29.4)	3 (50.0)	1.10	0.19 to 6.40
Splenomegaly	2 (11.8)	3 (50.0)	0.33	0.04 to 2.50
Ascites	1 (5.9)	1 (16.7)	0.60	0.03 to 11.27

Table 2. Results of Laboratory Tests in Children With Cystinosis

Tests	Mean Values
Complete blood count	
Leukocyte, × 10^9/L	13.3 ± 8.6 (4 to 38)
Erythrocyte, × 10^{12}/L	2.86 ± 1.00 (1.6 to 4.8)
Hemoglobin, g/dL	8.96 ± 3.20 (3.4 to 15.0)
Mean corpuscular volume, fL	85.78 ± 3.48 (72.5 to 106.0)
Platelet, × 10^9/L	234.62 ± 167.68 (53.0 to 454.0)
Serum chemistry	
Urea nitrogen, mg/dL	45.0 ± 36.0 (9 to 154)
Creatinine, mg/dL	3.84 ± 3.00 (0.70 to 9.80)
Sodium, mEq/L	133.0 ± 3.0 (127 to 141)
Potassium, mEq/L	3.90 ± 0.95 (2.2 to 6.4)
Calcium, mg/dL	8.59 ± 0.82 (7.0 to10.1)
Chloride, mEq/L	103.0 ± 13.0 (65 to 118)
Phosphate, mg/dL	7.16 ± 2.90 (4.0 to 13.6)
Liver function tests	
Alkaline phosphatase, IU	1017 ± 832 (130 to 3117)
Aspartate aminotransferase, IU	31.0 ± 17.2 (9 to 35)
Alanine aminotransferase, IU	19.0 ± 7.2 (10 to 31)
Prothrombin time, sec	19.5 ± 16.4 (13 to 60)
Partial thromboplastin time, sec	33.0 ± 6.9 (25 to 46)
Total bilirubin, mg/dL	2.58 ± 3.55 (0.6 to 7.9)
Direct bilirubin, mg/dL	3.27 ± 5.39 (0.1 to 9.5)
Total protein, mg/dL	6.52 ± 1.20 (4.9 to 8.6)
Albumin, mg/dL	3.56 ± 0.40 (2.9 to 4.1)
Venous blood gases	
pH	7.30 ± 0.11 (7.1 to 7.7)
PCO_2, mm Hg	26.0 ± 5.5 (16 to 35)
HCO_3, mEq/L	12.51 ± 3.80 (5.0 to 17.4)

DISCUSSION

The most frequent gastrointestinal manifestation in our case series was vomiting and in the second place was diarrhea. Overall, there was no significant difference in the frequency of gastrointestinal symptoms between those with and without end-stage renal disease. Elenberg and colleagues reported gagging/vomiting in 58 of 70 patients with nephropathic cystinosis that occurred either daily/intermittent, after medication, or by the sight of food alone.[2] Our patients had vomiting either intermittently or after cysteamine bitartrate prescription. Although vomiting was more frequent in those with end-stage renal disease, the difference was not significant.

One of our patients with a GFR of 50 mL/min had a complaint of dysphagia. No further evaluation had been performed in this patient to find the cause of swallowing dysfunction. In a study performed on 101 patients with cystinosis aged 6 to 45 years, Sonies and colleagues[5] found that oral, pharyngeal, and esophageal phases of barium swallowing were abnormal in one-third to three-quarters of the patients and detected that swallowing severity score and oral muscle composite score increased with the number of years without cysteamine therapy.

The majority of our cases had failure to thrive with some degrees of chronic kidney failure. This is an alarm for general physicians and pediatricians who take care of the infants and children on outpatient visits. Nephropathic cystinosis frequently presents with polyuria/polydypsia, failure to thrive, and rickets at ages less than 2 years. Unawareness of these presentations and delay in diagnosis and especially in starting appropriate therapy are a leading cause of progressive cystine accumulation in the kidney and other tissues.

One-third of our patients had hepatospelomegaly with normal liver function tests and 2 without organomegaly had ascites. Reviewing the literature revealed that one-third of patients nephropathic cystinosis had hepatomegaly by the age of 5 years, and in children older than 10 years, hepatomegaly was associated with normal liver function tests, resulting from hepatic veno-occlusive disease

secondary to cystamine therapy, toxic hepatitis, viral hepatitis, portal hypertension attributed to cirrhotic and noncirrhotic liver disease, and cholestasis.[3,4,6,10,11] Liver samples have shown infiltration of hepatic sinusoids with cystin-laden macrophages as a causative factor.

A significant number of our patients had abdominal distension, diarrhea, or constipation. In addition to the effect of electrolyte imbalance on gastrointestinal peristalsis, electromacroscopic study showed that children with nephropathic type of cystinosis had infiltration of cystine crystals in lysosomes, phagocytic cells, and lamina propria of the intestine, and even rectal suction biopsy had been suggested as a modality of diagnosis.[12] Rarely, the association of this disease with ulcerative colitis had been reported.[13]

Although the small sample size of our series and the presence of chronic kidney failure in the majority of the cases were the main restriction that made a major bias, this report could raise the awareness of the physician to have high sense of suspicious to cystinosis in infants who present with failure to thrive, polyuria, polydypsia, and rickets, especially in those who are the children of parents with a consanguineous marriage. Early recognition and therapy of cystinosis might postpone the process of kidney damage.

The second lesson was that the gastrointestinal manifestations were widely ignored in these children who dominantly presented with renal presentation. The third and the most important point was that the clinician had to rely on the report of bone marrow aspiration and corneal exam to confirm the diagnosis that is sometimes negative, depending on the duration of the disease and the experience of physician in recognizing crystals of cystine. Launching fibroblast and lymphocyte culture for early recognition of the disease and evaluation of the effective dosage of the cystine-removing drug should be considered. Additional prospective investigations are needed to delineate the pathogenesis of gastrointestinal abnormalities in patients with cystinosis.

CONCLUSIONS

Our study revealed a wide spectrum of gastrointestinal disturbances in children with cystinosis. Such findings should lead to greater awareness of the presence of gastrointestinal dysfunction in these children, encouraging prompt awareness evaluation, and treatment of more severely affected patients.

CONFLICT OF INTEREST

None declared.

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