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Urinary System and Renal Involvement in Children With Cystic Fibrosis

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Original Paper

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Introduction. A few data on the prevalence of renal involvement in cystic fibrosis and its spectrum in childhood is available. In the present study, we conducted a prospective study on children who had cystic fibrosis and evaluated their renal involvement. In fact, the aim of the study was to provide data on the clinical consequences of proper identification of kidney disease in a group of children with cystic fibrosis.
Methods. This prospective study was conducted on 55 consecutive patients with previous diagnosis of cystic fibrosis during a three-year period and at least 3 months to over 5 years or more follow-up. The inclusion criteria was the diagnosis of cystic fibrosis which was made by clinical presentation of cystic fibrosis and laboratory results. Initially, patients' medical records were reviewed and relevant data were collected. A 24-hour urine collection (or a random urine sampling in very young infants) was used to assess crystalluria and renal function was evaluated by blood sampling.
Results. Totally, 55 patients with cystic fibrosis were admitted in two hospitals with the mean age of 8.22 ± 5.66 years. GFR totally reduced in 34.5%. The overall prevalence of hypercalciuria was estimated to be 60%, while hyperoxaluria, hypocitraturia, and hyperuricosuria in 41.8%, 24.5%, and 47.3%; respectively.
Conclusion. Crystalluria is a common consequence of cystic fibrosis in childhood. The prevailing crystalluric finding includes hypercalciuria followed by hyperuricosuria, and hyperoxaluria. During disease GFR may be decreased due to several reasons such as nephrotoxic drugs usage.

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INTRODUCTION

Recent evidences have emphasized the association between cystic fibrosis and appearance of kidney injuries especially among children.[1,2] Following significant development in treatment of respiratory disorders and pancreatitis in cystic fibrosis, the life expectancy among patients has been considerably increased from 2 years to more than 30 years.[3,4] One of the main underlying factors affecting the progression as well as prognosis of the affected patients includes the presence of the CFTR gene polymorphism that encodes a polyprotein cystic fibrosis trans-membrane conductance regulator (CFTR), which functions as an ATP-responsive chloride channel in apical membrane of epithelial cells.[5] Because this gene is abundantly findable in various segments of the nephron especially in proximal tubule, the inactivation of CFTR can lead to renal insufficiency presents with proteinuria as well as nephrocalcinosis and hypercalciuria.[6] In this

regard, the overall prevalence of nephrocalcinosis and hypercalciuria is estimated to be 90% and 30% of affected patients, respectively emphasizing high risk for renal impairment in cystic fibrosis patients.[7] More interestingly, urolithiasis in these patients may result from hyperoxaluria originated from other clinical abnormal conditions such as fat malabsorption. Along with urolithiasis, patients with cystic fibrosis may be also found, but less commonly, with other renal disorders such as glomerulonephritis, and AA amyloidosis.[8-10] Totally, renal involvement in cystic fibrosis should be considered as an emergence; however a few data on the prevalence of renal involvement and its spectrum in childhood is available. In the present study, we report a series of children who had cystic fibrosis and some degree of renal involvement. In fact, the aim of this study was to provide data on proper identification of kidney disease in a group of children with cystic fibrosis.

MATERIALS AND METHODS

This prospective study was conducted on 55 consecutive patients with final diagnosis of cystic fibrosis who referred to Masih Daneshvari and Mofid Children's hospital in Tehran during 2012 to 2015. In this study, the diagnosis of cystic fibrosis was made if there were clinical presentations in addition to chloride concentration more than 60 mmol/L in sweet test according to the guidelines by the Gibson & Cooke methods in two separate tests. In addition, we confirmed pancreatic malabsorption by quantification of elastase-1 activity and fat droplet in stool sample. False positive cases such as anorexia nervosa, congenital adrenal hyperplasia, adrenal insufficiency, glucose-6-phosphatase deficiency, familial hypoparathyroidism, hypothyroidism, nephrogenic diabetes insipidus, pseudohypoaldosteronism, and Klinefelter syndrome were ruled out by history, physical examination, and appropriate laboratory tests. Initially, patients' medical records were reviewed, and relevant data were collected regarding baseline characteristics, anthropometric parameters, blood pressure on admission, and laboratory indices. Also, kidney ultrasonography was done and findings were highlighted. A 24-hour urine collection (or a random urine sampling in very young infants) was done to assess crystalluria. The methods of measurement of crystals in urine was as following: peroxidase-TOOS [N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine] method for uric acid, photometric method for calcium and citrate, colorimetric oxidase method for oxalate, and Jaffe's reaction for creatinine. GFR was calculated using the Schwartz formula and serum creatinine was measured by Jaffe method: "GFR (mL/min/1.73m^2) = (K) (height in cm) / serum creatinine (mg/dL).[11]

In this formula, "K" coefficient in infants under one year of age with LBW and infants with birth weight above 2.5 Kg under one year is 0.35 and 0.45, respectively. This number for young children and female patients in pubertal age is 0.55 and for male patients is 0.7.[12,13]

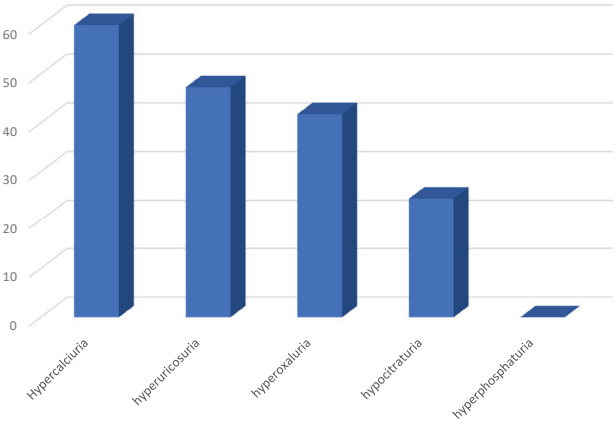
To assess the electrolyte abnormalities, their concentration was determined and venous blood gas analysis was done. The findings related to the *CFTR* mutation were also recorded if available. In ten cases genetic study confirmed the diagnosis.

Results were presented as mean ± SD for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. For the statistical analysis, the statistical software SPSS version 16 for windows was used.

RESULTS

Within three years of study, 55 patients with cystic fibrosis were admitted to these two hospitals with the mean age of 8.22 ± 5.66 years (ranged 4 months to 22 years). Follow up duration was five years. Even in some cases the follow up period was longer. Patients were visited on a monthly basis or every two months averagely. Cases with exacerbation or worsening of their condition were hospitalized. Treatments included antibiotics based on patients age and cultured microbial species. Nebulized treatments which were used were as following: inhaled antibiotics, hypertonic saline, and in some cases recombinant DNAase. Appropriate supplements, vitamins and diet were prescribed for CF patients. Physiotherapy was done and based on the patients' condition, traditional methods or appropriate devices were used. During admission, psychologic or psychiatric consultation might have been required. Appropriate vaccination was considered. We took patients' or parents' consent in advance. The study was approved by ethics committee of SBMU (The registration number is: IR.SBMU.MSP.REC.1397.559). Among patients,

52.7% were male (with a mean age of 7.20 ± 5.34 years) and 47.3% were female (with the mean age of 9.55 ± 5.81 years). The blood pressure was in the normal range in all subjects with no evidences of hypertension. Hematuria was a prominent finding in 5 patients (9.1%). Urine culture was negative in all patients. One patient (1.8%) showed bilateral fullness in ultrasonography. None of the patients had electrolyte disturbances. The details on demographic data and laboratory indices are summarized in Table. The most common electrolyte abnormalities were hyponatremia and hypokalemia.Venous blood gas analysis showed normal condition in 28 patients, while 5 patients were diagnosed as respiratory acidosis, 10 patients as respiratory alkalosis, 5 patients as metabolic alkalosis, and 7 patients as a mixed blood gas abnormality. GFR totally reduced (according to patients' age) in 14 patients (25.4%), while ranged 60 to 89 in 23.6%, and 15 to 30 in only 1.8%. The status of crystalluria is shown in Figure. The overall prevalence of hypercalciuria was estimated to be 60.0%, while hyperoxaluria, hypocitraturia, and hyperuricosuria diagnosed in 41.8%, 24.5%, and 47.3%; respectively. Decreased urine output was found in only one patient (1.8%).



It shows frequency of crystalluria in children with cystic fibrosis.

DISCUSSION

Despite low prevalence of symptomatic urolithiasis among patients with cystic fibrosis, the prevalence of hypercalciuria was shown to be notably high causing unexplained morbidities in these patients. It is thus mandatory to identify different aspects of renal involvement in the patients because of its adverse effect on life expectancy particularly among children due to their lower tolerability. In most studies the incidence and clinical status of renal involvement in cystic fibrosis

Details on Demographic Data and Laboratory Serum Indices in Children with Cystic Fibrosis

Parameter	Mean	SD	Minimum	Maximum
Weight, kg	20.53	11.39	2.8	52.7
Height, cm	116.7	29.98	55	161
Percentage of FTT	63.63 (35 cases)	-	-	-
Sweat Chloride, mmol/L	81.67	11.38	65	110
Urine Output, mL	1290.38	682.35	200	2700
Sodium, mEq/L	137.96	2.72	131	144
Potassium, mEq/L	4.24	0.45	3.1	5.5
Urea, mg/dL	18.34	6.33	4	34
Cr, mg/dL	0.65	0.15	0.3	0.9
Uric Acid, mg/dL	4.29	0.96	2.9	6.8
Calcium, mg/dL	8.87	0.59	7.6	10
Phosphorus, mg/dL	4.21	1.02	2.1	6.6
Alkaline Phosphatase	491.45	207.84	156	1124
Bicarbonate	24.98	24.56	16.6	44.4
PH	7.41	7.41	7.3	7.53
PCO_2	37.05	11.04	22	76.2
Urine Calcium	11	197	92.84	55.03
Urine Uric Acid	384.84	252.77	59	1072
Urine Citrate	324.7	221.71	74	902
Urine Phosphorus, mg	512.8	323.96	132	1620
Urine Protein, mg	92.69	72.44	11	282
Urine Cr, mg	385.61	200.02	66	743
GFR, mL/min/ 1.73 m^2	100.87	27.62	20.16	162

was based on histological assessments using renal biopsy. In one of the main studies by Abramowsky and Swinehart[11] on autopsies from both pediatric and adult patients, the main histological findings were related to glomerulomegaly, a mesangiopathic lesion, and tubulointerstitial disease frequently associated with acute and chronic tubular injury that were significantly associated with the severity of renal dysfunction. In the present study and aided by laboratory findings and sonography assessment, we showed high prevalence of crystalluria especially hypercalciuria and hyperuricosuria in children with cystic fibrosis. In our study, the dominant crystalluric finding was hypercalciuria found in about two-third of patients, while hyperoxaluria or hyperuricosuria was found in less than half of them. In fact, it seems that the existence of exocrine pancreatic dysfunction as a major risk factor for enteric hyperoxaluria may be revealed in about half of our patients. In contrast with other reports that showed increased prevalence of calcium oxalate and medullary nephrocalcinosis,[12] our results were negative.

Regarding renal functional status, reduced GFR was found in about a quarter of the children that was significant. We estimated the GFR based on creatinine clearance; however we showed reduced urinary output only in 1.8% of the patients. It is now agreed that the estimation of GFR using creatinine is not a reliable estimation of renal function. In fact, the assessment of renal sclerotic lesions as a serious renal change following cystic fibrosis may not be followed by only GFR estimation based on creatinine. Because accurate assessment of renal sclerotic lesions is of great help for clinicians who care for these patients, employing suitable and more valid tools to assess these changes is essential particularly in those who require receiving nephrotoxic immunosuppressive agents; As a result, limitation of our study was that we could not use an accurate method for GFR measurement such as DTPA (diethylenetriamine pentaacetate).

In conclusion, crystalluria is a common consequence of cystic fibrosis in childhood. The prevailing crystalluric finding includes hypercalciuria followed by hyperuricosuria, and hyperoxaluria. Thus, assessing the risk of crystalluria and also determination of its main predictors is essential to prevent deleterious effects on renal function especially in affected children.

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