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Original Article

Renal impairment in children with cystic fibrosis☆

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Abstract

Background: Due to the improvement in life expectancy in cystic fibrosis (CF), co-morbidities such as renal function impairment may be more frequent.
Aim: To determine the prevalence of renal disease in children with CF and to identify associated risk factors.
Methods: A single-center retrospective study analyzing the genetic, clinical and therapeutic characteristics of 112 children. The estimated glomerular filtration rate (GFR), microalbuminuria and lithiasic risk factors were assessed.
Results: The median calculated GFR (Schwartz) was 123, 161 and 155 ml/min/1.73 m^2 in children aged 1, 6 and 15 years, respectively. The cumulative dose of aminoglycosides was not correlated to GFR. Microalbuminuria was present in 22/38 patients. Hyperoxaluria was observed in 58/83 patients and was associated with a severe genotype, pancreas insufficiency and liver disease. Hypercalciuria, hyperuricuria and hypocitraturia were identified in 16/87, 15/83 and 57/76 patients, respectively.
Conclusion: Renal impairment in CF has various presentations. There appears to be low levels of renal impairment in children with CF. However, the risk of oxalocalcic urolithiasis is enhanced, and GFR may be underestimated by the Schwartz formula. Further studies using measured GFR techniques are thus warranted.
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Keywords: Cystic fibrosis; Child; Nephrotoxicity; Kidney disease; Urolithiasis; Antibiotics

1. Background

The life expectancy of patients with cystic fibrosis (CF) has dramatically increased over the past decades [1], raising the concern about the onset of new co-morbidities associated with CF such as diabetes mellitus and renal impairment. In the seventies, the average life expectancy in CF was approximately 14 years whereas in 2003 [2], more than 50% of the patients had reached the age of 25 years. The number of patients aged 40 years is also increasing, and the median survival of patients born in 2000 is expected to be above 50 years [3].

Therefore, the risk for renal impairment in patients with CF has become a reason for concern as indicated by a very recent review [4]. Indeed, these patients are at higher risk of developing urolithiasis and nephrocalcinosis. This has been illustrated by studies revealing increased urinary excretion of factors promoting lithogenesis (such as hyperoxaluria or hypercalciuria) and decreased urinary excretion of inhibiting factors such as citraturia [5–7]. Moreover, the use of nephrotoxic drugs in the treatment of pulmonary disease, such as antibiotics (in particular aminoglycosides) and non-steroidal anti-inflammatory agents, may lead to renal injury [8–10]. With improved life expectancy, the use of nephrotoxic drugs may increase over time, exposing presently young patients to greater

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cumulative doses at adult age. Co-morbidities such as diabetes and liver disease will also become more frequent in the next years, leading to even more complex treatment strategies [11]. Therefore, the prevention of renal impairment has become a crucial issue, in order to improve patient survival and quality of life.

To complicate matters more, patients with end-stage respiratory failure benefitting from lung transplantation have an additional risk of renal impairment. Indeed, chronic renal failure has been shown to be the most frequent non-infectious medical complication after lung transplantation [12]. Bech et al. also showed an early and important decrease in measured glomerular filtration rate in transplanted patients [13]. In some instances, further renal transplantation was required. In these studies, the decrease in renal function after transplantation was related to pre-existing renal impairment and the nephrotoxicity of calcineurin inhibitors. It is thus important to preserve renal function in patients with CF, from childhood to adult age, in order to optimize the conditions of their survival and to achieve the least minimal renal damage prior to transplantation.

Despite all of the above, there are limited data regarding renal impairment in children with CF. We hypothesize that in such a population, underlying renal disease might be more frequent than previously believed.

The aim of the present study was thus to determine the prevalence of various forms of renal disease in a population of children with CF, and to identify associated risk factors.

2. Methods

2.1. Population

A single-center retrospective study was conducted at the tertiary-care Paediatric Department of Bordeaux University Hospital, France. This study focused on the patients followed at the Paediatric Cystic Fibrosis Unit (Centre de Ressources et de Compétences de la Mucoviscidose, CRCM) between 1998 and 2008.

Overall, the children were examined on a monthly basis in the first year of life and every 3 months thereafter. A full clinical, imaging and laboratory health assessment was performed yearly.

Patients whose diagnosis was confirmed by molecular biology (two identified mutations) and/or by two positive sweat tests were included. Diagnosis was made prior to the age of 18 years and all patients were still being followed at the CRCM at the time of the study. Patients presenting with Cystic Fibrosis Transmembrane Regulator (CFTR) disease other than CF were excluded, as well as those who had settled down elsewhere during the study period (incomplete data).

Patients' data were collected up to May 2008, using medical files of the Paediatric CRCM of Bordeaux.

2.2. Data collection

The following data were recorded for each patient: date of birth, gender, history of meconial ileus, date of diagnosis of CF, genotype, follow-up period, Body Mass Index at 2, 5, 10 and 15 years. In patients who had undergone neonatal screening, the 4th day of life was considered as the date of diagnosis of CF.

Mutation screening for the CFTR gene was performed either by PCR and reverse dot-blot hybridization or by PCR-sequencing. Mutations were classified into three categories, according to the present knowledge regarding their expected phenotypic expression: severe, mild or unknown [14].

2.3. Definitions

Pancreatic insufficiency was defined as stool pancreatic elastase rate below 200 µg/g, as assessed by an ELISA test using monoclonal antibodies [15].

Liver disease was defined by the presence of at least one of the following features: clinically observed hepatomegaly for at least 6 months, liver enzyme levels above the upper limit of normal over a time span of at least 6 months (laboratory norms: ASAT 10 to 70 IU/ml, ALAT 5 to 40 IU/ml) and abnormal ultrasonography (heterogeneous or nodular liver, hepatomegaly and/or signs of portal hypertension) [16,17].

The diagnosis of diabetes mellitus was confirmed by an oral glucose tolerance test. Patients partially intolerant to carbohydrates were not classified as diabetic.

Chronic colonization by *Pseudomonas aeruginosa* was defined by at least 3 positive sputum tests for this bacteria and no negative test within the 6 months preceding the study. Patients with a history of primary infection already efficiently treated or running for less than 6 months were not noted for this feature.

The cumulative number of days of intravenous (IV) antibiotherapy (tobramycin, gentamycin, amikacin, netilmycin, vancomycin, teicoplanin and ciprofloxacin) and the cumulative number of months of inhaled antibiotherapy (colistin and tobramycin) received by the patients were also reported. IV aminoglycosides were always administered on a once-daily basis.

2.4. Renal investigations

GFR was recorded at 1, 3, 6, 9, 12 and 15 years using the Schwartz formula (GFR(schw)) or the UV/P formula (GFR(uv/p)). The Schwartz formula used was: [k × height (cm)] / plasma creatinine (µmol/l), with k=40 before 2 years of age, k=49 from 2 to 13 years of age, and k=62 for males (49 for females) after 13 years of age [18]. The UV/P formula is a calculated GFR method defined as [(urinary creatinine × urinary 24-hour volume) / plasma creatinine] × (1.73/body surface area). The blood and urine samples used for the determination of GFR were essentially obtained during hospitalization. GFR impairment was defined as a filtration rate below 90 ml/min/1.73 m^2.

The urinary albumin/creatinine ratio, performed in fresh urine samples to assess microalbuminuria, was considered to be abnormal according to the European Society for Paediatric Nephrology definition (>5 mg/mmol if age is <2 years, >2 mg/mmol if age is ≥2 years) [19]. Assays were performed using a Modular auto-analyzer (Roche/Hitachi) by the ELISA method

for albumin, and by the kinetic colorimetric method for creatinine.

Kidney size and cortico-medullar differentiation were assessed by ultrasonography in the Department of Radiology of Bordeaux Hospital. Lithiasic risk factors were estimated by the oxalate/creatinine, calcium/creatinine, uric acid/creatinine and citrate/creatinine ratios, during a cristalluria test (single urine sample) or a 24-hour urine sample. Hypocitraturia was defined by a citrate/creatinine ratio of <0.3 mmol/mmol. Hyperoxaluria, hypercalciuria and hyperuricuria were defined according to the patient's age as in previously reported data [19,20]. Urinary oxalate and citrate were measured by High Performing Liquid Chromatography and "step gradient" technique. Urinary calcium and uric acid were measured by the ELISA method and enzymatic method respectively, using a Modular auto-analyzer. The presence of urolithiasis and nephrocalcinosis was assessed by ultrasonography. Patients were considered at risk of urolithiasis if at least one risk factor was found.

2.5. Statistical analysis

Statistical analysis was performed using NCSS® software (Kaysville, Utah, USA). Data are presented as percentages for categorical variables and mean±SD or median and interquartile range for continuous variables. Pearson or Spearman correlations test was used. In order to examine the association between some exposure variables (age, genotype, liver disease, pancreatic insufficiency, diabetes, chronic colonization by *P. aeruginosa* and cumulative number of days of antibiotics) and the dependent variables (hyperoxaluria and hypercalciuria, respectively, defined each as a binary outcome variable), multivariate logistic regression models were performed using a stepwise backward procedure. The association between the exposure variables and the presence of hyperoxaluria and hypercalciuria, respectively, were expressed as Odds Ratio (OR). In the final model p-values <0.05 were considered significant.

3. Results

A total of 112 patients were included in the study. The main clinical features of the population are reported in Table 1.

Table 1
Patient characteristics.

Variables	Total (n=112)
Sex (boys/girls)	59/53
Age at diagnosis (months)	4.3 [0.3–57.8]
Age at the end of study (years)	8.3 [3.9–13.0]
Follow-up period	
Before CRCM	49/112 (44)
CRCM	27/112 (24)
Neonatal screening	36/112 (32)
Follow-up (years)	6 [3.0–10.4]
Body Mass Index (kg/m^2)	
2 years	15.5 [14.9–16.6]
5 years	15.2 [14.5–16.3]
10 years	16.2 [14.8–18.0]
15 years	19.0 [16.7–20.8]
Genotype	
p.508.del/p.508.del	51/112 (46)
p.508.del/other	44/112 (39)
Other/other	16/112 (14)
p.508.del/unknown	1/112 (1)
Genotypic severity	
Severe/severe	93/112 (83)
Severe/mild	17/112 (15)
Mild/mild	1/112 (1)
Severe/unknown	1/112 (1)
Meconial ileus	13/112 (12)
Pancreatic insufficiency (n=97)	78/97 (80)
Liver disease	29/112 (26)
Diabetes mellitus	5/112 (4)
Colonization with *Pseudomonas aeruginosa*	23/112 (21)
Intravenous antibiotics	57/112 (51)
Inhaled antibiotics	70/112 (63)

CRCM: Centre de Ressources et de Compétences de la Mucoviscidose.
n (%) or median [IQR].

3.1. Glomerular filtration rate (GFR) according to the estimated methods

Throughout the overall follow-up period, transiently decreased GFR(schw) (less than 90 ml/min/1.73 m^2) was observed in 21 patients (19%), mostly prior to the age of 3 years. At the end of the study, no patient presented with a decreased GFR(Schw) (median [IQR] 173 [150–197] ml/min/1.73 m^2) and there was no difference in GFR between children with "severe" and "non-severe" mutations (p=0.18). GFR(schw) values are reported in Fig. 1 according to the patients' age.

Data regarding GFR(uv/p) were only available for 24 patients. No correlation was found between GFR values obtained according to the Schwartz or UV/P formulae (n=41, r=0.12, p=0.45). For 30% of the values, GFR was overestimated by the Schwartz formula, whereas UV/P values were less than 90 ml/min/1.73 m^2 (Fig. 2).

Although mean GFR(uv/p) was 105±43 ml/min/1.73 m^2 (n=24), 14 patients had presented a GFR(uv/p) less than 90 ml/min/1.73 m^2. Five of these patients showed regularly

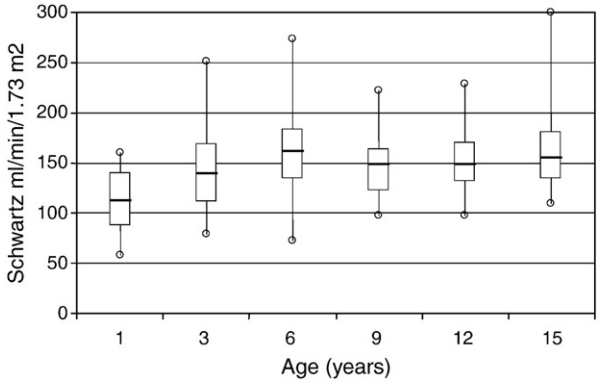

Fig. 1. Calculated GFR according to Schwartz formula. Results are median [IQR] ml/min/1.73 m^2, according to age (1 year n=44; 3 years n=54; 6 years n=46; 9 years n=34; 12 years n=28; 15 years n=16). Small circles correspond to the range.

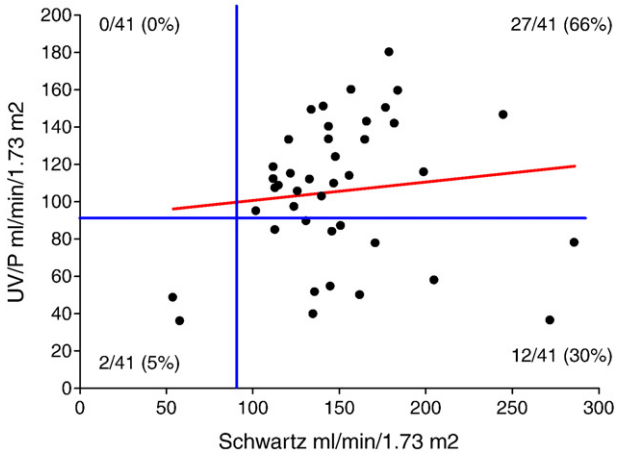

Fig. 2. Correlation between GFR(schw) and GFR(uv/p). Results are in ml/min/1.73 m^2. $n=41$ values for 24 subjects ($r=0.12$, $p=0.45$). UV/P=[(urinary creatinine×24-hour urinary volume)/plasma creatinine]×(1.73/body surface area). Schwartz formula=[(k×height)/plasma creatinine]×(1.73/body surface area). Horizontal line=UV/P value of 90 ml/min/1.73 m^2. Vertical line=-Schwartz value of 90 ml/min/1.73 m^2.

decreasing GFR over the preceding 3 years, all of whom receiving regular intravenous antibiotic courses. This event seemed to occur more likely after the age of 10–11 years.

However, there was no significant correlation between GFR (schw) or GFR(uv/p) and the cumulative number of days of aminoglycosides received by the patients ($r=0.18$, $p=0.08$ and $r=0.008$, $p=0.9$, respectively) (Fig. 3). The results were similar regarding all other antibiotics administered, including via the inhaled route (data not shown). Noteworthy, a strong inverse relationship between GFR(uv/p) and the cumulative dose of netilmycin was observed in a very small number of patients ($n=4$, $r=-0.97$, $p=0.03$) (data not shown).

3.2. Microalbuminuria

Increased albumin/creatinine ratio was observed in 22/38 (58%) patients. The mean age microalbuminuria was observed was 8.4±4.8 years. The median values were 6.9 mg/mmol (normal value<5 mg/mmol) and 2 mg/mmol (normal value<2 mg/mmol) in children under or above 2 years old, respectively.

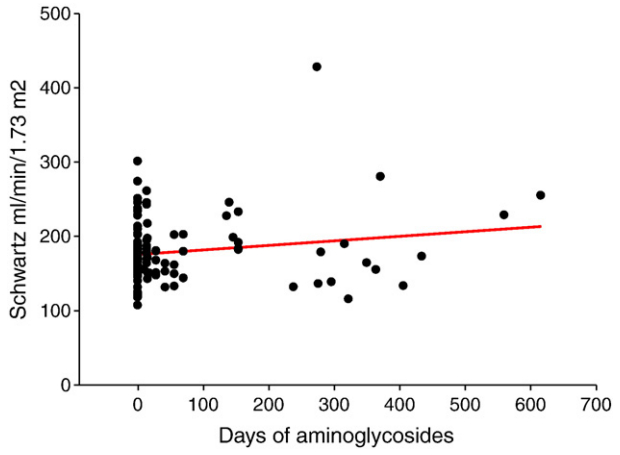

Fig. 3. Correlation between GFR(schw) and the number of days of aminoglycosides administered to all patients ($n=105$, $r=0.18$, $p=0.08$), including those who had never received any antibiotics.

3.3. Prevalence of urolithiasis and lithiasic risk factors

None of the patients presented with a symptomatic episode of urolithiasis. However, urolithiasis was diagnosed by ultrasonography in 2/109 (2%) patients.

One patient had numerous bilateral millimetric lithiasis identified at the age of 3 months, with cristalluria analysis revealing only isolated hypocitraturia. Another patient presented with an asymptomatic non-obstructive pyelic urolithiasis (main axis, 11 mm) at the age of 12 months. Cristalluria analysis showed isolated hyperoxaluria. Regarding urolithiasic risk factors, hyperoxaluria was observed in 58/83 (70%) patients, hypocitraturia in 57/76 (75%) patients (median age at diagnosis 7.6 years and 9.7 years, respectively), hypercalciuria in 16/87 (18%), and hyperuricuria in 15/83 (18%) (Fig. 4). Sixteen percent of patients had both hyperoxaluria and hypercalciuria. Hypocitraturia was associated with hyperoxaluria and hypercalciuria in 6/76 (8%) patients. Hyperoxaluria was associated with a severe genotype (OR=2.15, 95% CI (1.75–20.35)), pancreatic insufficiency (OR=2.16, 95% CI (1.74–20.99)) and liver disease (OR=1.46, 95% CI (1.17–26.43)). Hypercalciuria was associated with liver disease (OR=2.59, 95% CI (1.01–11.01)). Values of the oxalate/creatinine ratio are shown in Fig. 5, according to the patient's age.

4. Discussion

The present study, using the Schwartz formula, did not show impaired GFR irrespective of the children's age group. Moreover, the correlation between Schwartz and UV/P GFR was poor. The cumulative dose of aminoglycosides was not correlated to GFR. Microalbuminuria was present in 58% of patients. Hyperoxaluria was observed in 70% of patients and was associated with a severe genotype, pancreas insufficiency and liver

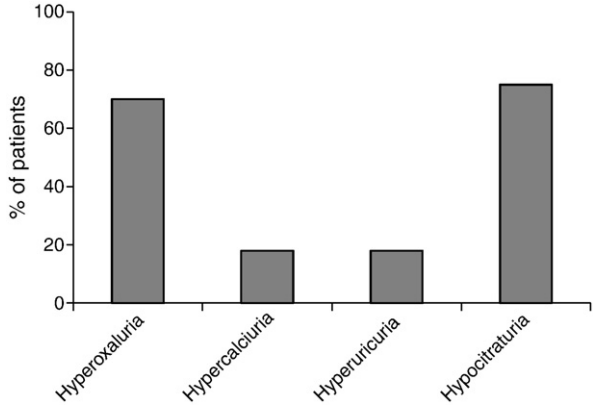

Fig. 4. Prevalence of main lithiasic risk factors. Oxaluria ($n=83$), calciuria ($n=87$), uricuria ($n=83$) and citraturia ($n=76$).

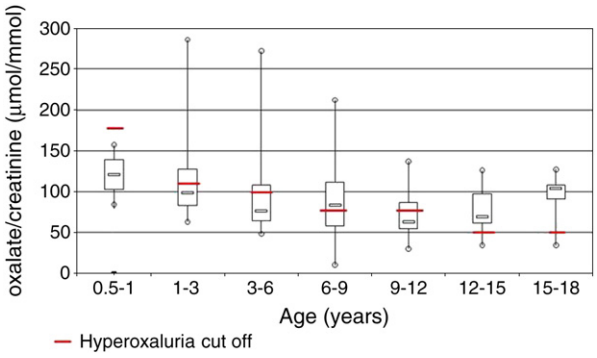

Fig. 5. Prevalence of hyperoxaluria according to age. Results are expressed in median [IQR] of oxalate/creatinine ratio µmol/mmol, with extremities of the boxes being minimal and maximal values. For 0.5–1 year old $n=2$, 1–3 years $n=18$, 3–6 years $n=29$, 6–9 years $n=24$, 9–12 years $n=25$, 12–15 years $n=21$, 15–18 years $n=5$.

disease. Hypocitraturia, hypercalciuria and hyperuricuria were identified in 75%, 18% and 18% of patients, respectively.

GFR impairment appears to be low in children with CF, irrespective of nephrotoxic antibiotic administration. However, the most widely-used method for GFR estimation, the Schwartz formula, was initially assessed in a few healthy children only [18] and may not be reliable for the early detection of impaired GFR. Indeed, some authors have shown a 20% overestimated GFR with this formula compared to inulin clearance, and only an 80% sensitivity of this formula to screen for GFR less than 90 ml/min/1.73 m2 [21]. In paediatric allograft recipients, this overestimation may attain 35% [22]. Reasons for erroneous estimations of GFR by the Schwartz formula in children with CF are numerous. First, the use of factor *k* in the numerator has not been assessed in this specific population. A study in children with chronic kidney disease that compared an optimized form of the Schwartz equation with a measured iothalamate GFR showed that the error of the GFR estimated by the Schwartz formula approximated ±20 ml/min per 1.73 m² [23]. These estimation errors may be substantially higher when creatinine calibration differences from laboratory to laboratory are not corrected. Second, the plasma creatinine level in the denominator may depend on diet, muscle mass, drug interaction and laboratory problems such as colorimetric interferences. Also, decline in hepatic function, observed in some patients with CF, may result in decreased creatine production and lower plasma creatinine levels.

The UV/P formula was another method used for the estimation of GFR. In the present study it showed decreased GFR in 14/24 patients, with a tendency to occur after the age of 12 years (9/14). This method has previously been applied in an adult CF cohort by Al-Aloul et al., who showed that 42% of patients had decreased GFR [9]. These results are compatible with the hypothesis that renal impairment in CF is of multifactorial origin, increasing over time and thus easier to detect in older patients. Although some recent studies have shown a strong correlation between measured creatinine clearance and GFR calculated estimating formulae in adults with CF [24], the different formulae for estimated GFR don't seem to be reliable for accurate assessment of renal function in children with CF [25]. The early diagnosis of GFR impairment in children with CF is thus difficult with the estimated method commonly available. However, because of the numerous factors that could affect renal function in the long term (dehydration, infections, nephrotoxic drugs, diabetes, hyperoxaluria…), a proper assessment is of capital importance. Thus, monitoring of renal function should be performed using gold standard methods such as inulin or Cr51 EDTA clearances, known to be reliable and reproducible [21].

Microalbuminuria was observed in 58% of patients (22/38), vs. 32% in a recent study including 40 adults with CF (without diabetes mellitus) [26]. Primary impairment of the glomerular filter is doubtable in CF since CFTR is not expressed in the glomerule. However, secondary impairment may be explained by chronic inflammation, repeated infections (glomerulonephritis caused by immune complex formation) [27], or nephrotoxicity of antibiotics [9]. Unfortunately, the absence of prospective collection of albuminuria in our study does not allow concluding on the reliability of microalbuminuria as an early sign of glomerular impairment in children with CF.

The prevalence of urolithiasis was lower in our study (2%) compared to previous reported data including both adults and children (3–6%) [28]. The early onset of lithiasis, within the first year of life for both our patients, contrasts with previous studies in which the first urolithiasic episode occurred in adolescents or young adults, and in only one five-year old child [28,29]. In the present study, one patient presented with multiple bilateral microlithiases at the age of 3 months, with the only risk factor identified being isolated hypocitraturia. A similar case of nephrocalcinosis with isolated hypocitraturia has previously been reported in a patient older than 15 years [5].

The prevalence of hyperoxaluria was greater than in former studies including both children and adults with CF (70% vs. 40 to 65%) [5,7]. Noteworthy, only one patient presented with a lithiasic complication. Hyperoxaluria may occur very early as observed in the present study (two children prior to the age of 6 months, and 50% of patients between 1 and 3 years old). This justifies the assessment of the oxalate/creatinine ratio as soon as possible, once the diagnosis of CF is established. The correlation between the occurrence of hyperoxaluria and the presence of severe CFTR mutations and pancreatic insufficiency may be explained by the fact that the severe mutations are strongly associated with pancreatic insufficiency, which results in malabsorptive hyperoxaluria. Indeed, digestive tract calcium exhibits great affinity for excess fatty acids and its binding to oxalate is thus disordered, allowing for enhanced soluble oxalate intake [30]. Moreover, these mutations cause more severe respiratory disease, with a greater need for IV antibiotics, leading to the destruction of *Oxalobacter formigenes* within the digestive tract. In a normal situation, this gram-negative bacillus absorbs oxalate in order to produce ATP, thus contributing to the limitation of oxalate intake. A lack of intestinal *O. formigenes* would constitute an additional risk of absorptive hyperoxaluria in patients with CF [7,31]. Thus, hyperoxaluria should be considered an important lithiasic risk factor, with an early onset and a high frequency among children with CF, justifying early screening and appropriate management.

In the present study, an increased urinary calcium excretion was observed in 18% of patients. These results are similar to those reported by other studies (12–20%) [5,29]. Hypercalciuria may be explained by mild intermittent hyperparathyroidism due to a lack of vitamin D [28] or to proximal tubule antibiotic toxicity leading to renal loss of phosphorus [29]. Moreover, increased sodium excretion (due to oral supplementation) in the proximal tubule induces parallel urinary calcium excretion [32].

Hyperuricuria in our study was observed at a lower level than in previous studies (18% vs. 25–55%) [5,6]. High protein diet and purine-rich pancreatic enzyme supplements may represent risk factors for enhanced urinary uric acid excretion in CF, which promotes formation of oxalocalcic stones.

Hypocitraturia in CF may be linked to stool bicarbonate loss leading to metabolic acidosis, which increases citrate reabsorption by the proximal tubule. In the present study, we noted a higher rate of hypocitraturia in patients compared to the literature (75% vs. 22–55%) [6,7]. Moreover, the observation of a 3-month-old patient with multiple bilateral urolithiases and isolated hypocitraturia should encourage early screening and adequate treatment.

A low level of urinary creatinine may be expected in CF, which would artificially increase creatinine dependent urinary ratios. However, the high prevalence of hyperoxaluria and hypercitraturia observed in the present study seems not to be related to the use of oxalate/creatinine and citrate/creatinine ratios. Indeed the prevalence of two other lithiasic risk factors (hypercalciuria and hyperuricuria) also estimated using creatinine ratio is consistent with results from others studies using a mmol/kg/day rate [5,29].

5. Conclusion

In summary, this study showed an increased risk of oxalocalcic urolithiasis in children with CF. Irrespective of nephrotoxic antibiotic administration, there appears to be low levels of renal impairment. However, GFR may be underestimated, due to a lack of paraclinical tools specifically adapted to this population. Further studies using optimal methods of glomerular filtration rate measurements are thus warranted. Screening for renal impairment, as early as in infancy, may be appropriate, since early intervention will preserve optimal renal function later in life.

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