Néphrocalcinose chez l'enfant Tunisien

Nephrocalcinosis in Tunisian children

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RÉSUMÉ

Prérequis: La néphrocalcinose est rare chez l'enfant. Les étiologies sont multiples. Le but de ce travail était de déterminer les étiologies de néphrocalcinose chez l'enfant tunisien.

Méthodes : Il s'agissait d'une étude rétrospective portant sur les cas de néphrocalcinose dans le service de pédiatrie de l'hôpital Charles Nicolle de Tunis sur une période de 10 ans (2001-2010).

Résultats : il s'agissait de 40 enfants. L'âge moyen était de 3,5 ans. Les symptômes et les signes cliniques les plus fréquents étaient un retard de croissance dans 42,5% des cas et une hématurie microscopique dans 53,8% des cas. Le diagnostic positif de néphrocalcinose a été porté sur l'échographie rénale. Les étiologies étaient dominées par l'hyperoxalurie primaire de type 1 (65% des cas) et l'acidose tubulaire distale (20% des cas). L'évolution vers l'insuffisance rénale terminale a été notée dans 18 cas.

Conclusion: l'hyperoxalurie primaire était l'étiologie prédominante de néphrocalcinose; un diagnostic précoce ainsi qu'un traitement précoce permettrait de limiter la dégradation de la fonction rénale.

Mots-clés

Néphrocalcinose, enfant, insuffisance rénale, hyperoxalurie, acidose tubulaire distale.

SUMMARY

Background: Nephrocalcinosis is rare in children. Its etiologies are multiple. The aim of this study was to analyze the etiology of nephrocalcinosis in Tunisian children.

Methods: This retrospective study was conducted in the department of pediatrics in Charles Nicolle Hospital during a period of 10 years (2001-2010).

Results: There were 40 children. The mean age was 3.5 years. The most common signs and symptoms at presentation were growth retardation (42.5%) and hematuria (53.8%). At presentation, renal failure was detected in 70% of patients. The diagnosis of nephrocalcinosis was performed by ultrasonography. The etiology of nephrocalcinosis included primary hyperoxaluria type 1 (65%) and distal renal tubular acidosis (20%). A progression to renal insufficiency was observed in 18 cases.

Conclusion: Primary oxaluria is the principal cause of nephrocalcinosis; early diagnosis and treatment are mandatory as they help limiting renal function deterioration.

Key-words

Children, hyperoxaluria, nephrocalcinosis, renal insufficiency, renal tubular acidosis.

Nephrocalcinosis (NC) is characterised by the deposition of calcium in the kidney parenchyma and the tubules. Asymptomatic in the majority of cases, nephrocalcinosis is often discovered incidentally during a routine ultrasound examination [1]. Nephrocalcinosis is a syndrome rather than a specific condition. Hence, the etiology must absolutely be found [2]. Its causes are multiple. NC is usually secondary to systemic metabolic and renal tubular disorder [3]. Systematic diagnosis evaluation in all children with NC should be done to elucidate the underlying etiology and to preserve renal function in addition to an initiation of a specific therapy. Kidney function is usually normal at diagnosis but a progressive renal failure develops slowly ensuing complete kidney destruction. The aim of this study was to evaluate the etiology of nephrocalcinosis in children who were referred to our department and compare our results with the literature.

METHODS

In this retrospective study, profiles of 40 children with nephrocalcinosis admitted to the department of Pediatric Nephrology in Charles Nicolle Hospital were studied during 2001-2010. Premature infants were excluded from the study. Patient's demographics, clinical, laboratory findings, underlying etiology and outcome were documented. Etiology of NC was determined by biochemistry tests and imaging depending on disease.

Initial investigations included blood pH, and blood levels of urea, creatinine, electrolytes, calcium, phosphorus, magnesium and uric acid. Urinay excretion of calcium, phosphorus, oxalate, uric acid, magnesium citrate, and crystalluria were done. Glomerular filtration rate (GFR) was expressed as creatinine clearance calculated by the Schwartz formula. Hypercalciuria was defined as a urinary Calcium excretion >4 mg/kg/day in collected samples or urinary Calcium/creatinine ratio >0.8, 0.4, 0.2 mg/mg in children aged < 6 months, 6-12 months, 1-2 years, and >2 years of age, respectively, in urine samples. Hyperoxaluria was defined as a urinary oxalate excretion>0.7 mmol per 1.73 m² per day or urinary oxalate/ creatinine ratio>0.13, 0.07, 0.08 mmol/mmol in children aged < 1 year, 1-4 years, >5 years of age, respectively, in urine samples. Direct urinary system X-ray and abdominal ultrasonography examination were performed on all patients.

Primary hyperoxaluria was diagnosed in patients having a high urinary excretion of oxalate and the DNA test, confirming that diagnosis, was done on 3 patients; distal renal tubular acidosis (RTA) in those with hyperchloremic metabolic acidosis (pH<7.35, bicarbonate<18mEq/l), hypokalemia, hypercalciuria, high urine pH(>5.5); idiopathic hypercalciuria in those having a high level of urinary calcium, with absence of other tubular defects and normal blood levels of calcium; primary hypomagnesaemia with hypercalciuria in those with hypomagnesaemia(<0.6mmol/l), urinary magnesium wasting and hypercalciuria.

Determination of the cause of NC was followed by specific therapy, wherever possible. Vitamin B6 was given for the treatment of hyperoxaluria. Patients with distal RTA received alkaline supplements with potassium while those with idiopathic hypercalciuria were administrated a low-sodium diet and thiazide diuretics. Patients with primary hypomagnesaemia received magnesium and thiazide diuretics.

All data were analyzed using SPSS program. We used X2 or Ficher's exact test for comparison of two proportions from independent groups. The Student t test was used to compare means. P<0.05 was considered to be statistically significant.

RESULTS

The mean age at the time of diagnosis was 3.5 (range 0.1-12.5) years, 21 were boys. Relevant clinical manifestations are given in table 1. Failure to thrive was noted in 5 patients. Psychomotor retardation was observed in 5 patients. One or more urinary tract infections were reported in 9 patients. A positive family history of calculi or NC was present in 42.5%. At presentation, GFR was≥ 90 ml/min/1.73 m² in 14 (35%) patients. Urinary oxalate excretion was elevated in 16 patients. Hypercalciuria was present in 14 patients. The etiologies of the NC are transcribed in Table 1.

Table 1: Clinical manifestations in children with nephrocalcinosis

Ligne SE/SI	Nombre des yeux (%)	Acuité visuelle moyenne log MAR
Absente	61 (30,9%)	0,65
Discontinue	71 (36,36%)	0,23
Présente	64 (32,74%)	0, 08
		p < 0.001

Table 2 : Etiologies of nephrocalcinosis

Etiologies	number	percentage
Primary hyperoxaluria	26	65%
Distal renal tubular acidosis	9	22.5%
Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis	3	7.5%
Idiopathic hypercalciuria	2	5%
Total	40	100%

The mean age of patients with primary hyperoxaluria type 1 (HP1) at diagnosis was 4.3 years (1 month-12.5 years) and the mean duration of follow-up was 3.5 years (1 month -10 years). Consanguinity was noted in 80.7% of cases. Nephrolithiasis was present in 61.5% of cases.

The urinary oxalate / creatinine was high (57.6%) with a mean value of 0.561 (0,186- 1,554). The oxaluria was high in 38.4% of cases with a mean of 1.075 (0.119 to 2.637). Oxalemia done for 2 patients with end-stage renal disease (ESRD), were 552 and 3204 mmol/l. Crystalluria revealed the presence of whewellite 1 crystals in 7 cases. The genetic study was conducted on 3 patients and confirmed the presence of alanine transferase glutamyl xanthine I244T mutation. At diagnosis, 57.6% had renal failure. Pyridoxine has been used in 73% of cases and 26.3% of patients were pyridoxine-sensitive. The evolution to ESRD was noted in 34.7% of cases. Six patients died.

We reported 9 cases of RTA. The mean age at presentation was 12 months (2 months- 4 years). Parental consanguinity was reported in 6 cases. Growth failure was observed in 6 cases. Rickets was observed in 3 cases. An association with urolithiasis was noted in one case. Improved growth was noted in 6 cases. Only one patient progressed to kidney failure.

We collected three cases of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC).

The mean age at presentation was 5.3 years (1.5-10). Relevant clinical manifestations were: neonatal seizures (1 case), index case (1 case) and abdominal pain (1 case). One patient had renal failure. The evolution to renal failure has been reported in two other cases.

Two patients had idiopathic hypercalciuria and were respectively 9 and 12 years old. Renal function was normal in both cases. Nephrolithiasis was observed (in both cases). The evolution was marked by the NC stabilization in one case and by its deepening in the second case. Renal function remained normal in both cases.

We found no statistically significant link between the type of nephrocalcinosis and the progression to chronic kidney disease (CKD) (p = 0.72). CKD was observed in 68.2% of patients with metabolic disorders, and 31.8% of those with tubulopathy. There was no statistically significant link between the etiology of nephrocalcinosis and the progression to CKD (p = 0.87). The link was not statistically significant between the age of revelation of nephrocalcinosis and the progression to CKD (p = 0.77).

DISCUSSION

Nephrocalcinosis is a rare disorder affecting children. It is characterized by an aberrant deposition of calcium in the kidney parenchyma. As nephrocalcinosis is only a symptom, not the disease itself, an underlying pathology must be identified. Their causes are multiple, but the majority involves metabolic disorder, generally of genetic or iatrogenic origin, increasing the urinary excretion of calcium or oxalate. In our study, primary hyperoxaluria was the main cause of nephrocalcinosis. It represented 65% of cases followed by distal renal tubular acidosis. In fact, the distribution of etiologies of nephrocalcinosis varies from one ethnic group to another. In several countries, the causes were prevailed by distal renal tubular acidosis. In the series of Ronnefarth et al [4] on 152 children, hypercalciuria was the most common cause affecting 34% of patients.

We collected 40 cases of nephrocalcinosis over a period of 10 years. This attests to the rarity of the pathology in question. The clinical presentation is nonspecific. Growth failure and developmental delay are the most common clinical manifestations [5]; within our study about half of our patients had growth retardation.

The primary hyperoxaluria type 1 is an autosomal recessive disorder, caused by an enzyme deficiency in liver peroxisomes [6, 7]. The infantile form is a particularly severe form and in 80% of cases, at diagnosis, patients have kidney failure. The primary hyperoxaluria was the main etiology of nephrocalcinosis in children, within our study. HPI, although rare, is quite common in our country, its average prevalence was estimated at 5.5 per million inhabitants and the average incidence at 0.23 per million population [8]; This could be explained by the high rate of inbreeding in our country, also observed in our study (77.5% of cases). Children with primary hyperoxaluria have a significant risk of developing kidney failure. At diagnosis, 10-40% of children were at the terminal stage [9-11]. Gargah et al [12] reported in their study a rate of ESRD by 27% at diagnosis with a higher incidence in the infantile form [6]. The genetic study was performed on 3 patients showing mutations I244T. This is the predominant mutation in Tunisia [13]. Mutation of 33_34ins C was detected in 32% of patients of Nagara et al study. [14] Advances in genetics allow diagnosis of HPI and establish an early treatment to reduce progression to CKD, as it allows prenatal diagnosis. The combined hepatorenal transplantation is the only therapeutic alternative to dialysis [15], which, unfortunately, is not yet practiced in Tunisia.

Distal tubular acidosis is the most common cause of nephrocalcinosis in children [16, 17,18]. However, it was the 2nd cause in our series. Bajpai [19] found that, at presentation, all patients with distal RTA had growth retardation. A growth improvement in a well conducted treatment was noted. Bajpai et al reported that the size at diagnosis and the degree of acidosis were factors affecting the growth improvement. In our study, growth retardation was noted in 75% of patients.

Idiopathic hypercalciuria is a common cause of nephrocalcinosis in children. It affects 13-34% of children with nephrocalcinosis [4, 20]. An investigation should be conducted to rule out other causes that may be associated with hypercalciuria. In our study, the etiology was rare since it affected only two patients. Other causes of nephrocalcinosis are rare, as objectified in our study. CKD depends on the severity of

nephrocalcinosis, its etiology and the rapidity of medical care provision. The evolution to ESRD is closely related to the underlying etiology. Indeed, it is inevitable in the HP1 [9, 10] and FHHNC syndrome [21-23]. However, patients with HCI or ATD keep a satisfactory and long-lasting renal function with a creatinine clearance of> 60 ml / min / 1.73 m2 [16]. Within our study, there was a non-statistically significant relation between the etiology and the progression to CKD. This could be explained by the low number of patients.

Our study has several limitations: it is a retrospective records analysis which reduces the reliability of the data collections; the number of patients is low and the monocentric nature of our study limits the extrapolation of our results.

CONCLUSION

In our country, primary hyperoxaluria remains the main etiology of the CN .We insist on the importance of molecular biology allowing to make a diagnosis of an index case in family members and thus providing an early treatment to limit the progression to CKD.

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