Monogenic urinary lithiasis in Tunisian children: 25 years' experience of a referral center

Lithiase urinaire monogénique chez l'enfant tunisien : Expérience de 25 ans d'un centre de référence

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Abstract

Objective: To describe the clinical, biochemical and evolutive profile of monogenic urinary lithiasis in Tunisian children followed up in a reference service, during a 25 years period.

Methods: This was a single-center retrospective observational study of children with urolithiasis, conducted in the pediatric nephrology department in Charles Nicolle Hospital, Tunis, Tunisia over 25 years (January 1st, 1996 to December 31, 2020). Children≤18 of age with urolithiasis with or without nephrocalcinosis related to a monogenic disease were included in our study.

Results: A total of 66 children were included in our study. Patients were 5.92±3.48 years of age at the time of urolithiasis diagnosis, and 5.33±3.66 years of age at the time of the underlying pathology diagnosis. The inherited urolithiasis disorders found in our series were: primary hyperoxaluria in 44 cases, cystinuria in 9 cases, Lesch Nyhan syndrome in 5 cases. Renal tubular acidosis was found in 3 cases, and hereditary xanthinuria in 2 cases. Bartter syndrome, adenine phosphoribosyltransferase deficiency and Hereditary hypophosphatemic rickets with hypercalciuria were found in 1 case each. After an average follow-up of 6.45±3.79 years, six patients were in end-stage renal disease. Three patients had died, all of them being followed for primary hyperoxaluria type 1.

Conclusions: Monogenic urinary lithiasis, although rare, are most likely under-diagnosed in countries with high consanguinity such as Tunisia. The screening of these diseases seems to be of primary importance because of their significant morbidity.

Key Words: Nephrolithiasis, Hereditary, Pediatrics, Genes, Chronic Kidney Disease, Prognostic, Tunisia

Résumé

Objectif : Décrire le profil clinique, biochimique et évolutif des lithiases urinaires monogéniques chez les enfants Tunisiens suivis dans un service de référence, au cours d'une période de 25 ans.

Méthodes : Il s'agissait d'une étude rétrospective monocentrique menée au service de néphrologie pédiatrique de l'hôpital Charles Nicolle, Tunis, Tunisie sur 25 ans (1er janvier 1996-31 décembre 2020). Les enfants dont l'âge était ≤ 18 ans présentant une néphrolithiase avec ou sans néphrocalcinose liée à une affection monogénique ont été inclus dans notre étude.

Résultats : Au total, 66 enfants ont été inclus dans notre étude. Les patients étaient âgés de 5,92±3,48 ans au moment du diagnostic de la lithiase urinaire, et de 5,33±3,66 ans au moment du diagnostic de la pathologie sous-jacente. Les maladies lithiasiques retrouvées dans notre série étaient : l'hyperoxalurie primaire dans 44 cas, la cystinurie dans 9 cas, le syndrome de Lesch Nyhan dans 5 cas. Une acidose tubulaire rénale était retrouvée dans 3 cas, et une Xanthinurie héréditaire dans 2 cas. Le syndrome de Bartter, le déficit en adénine phosphoribosyltransférase et le rachitisme hypophosphatémique héréditaire avec hypercalciurie ont été retrouvés dans 1 cas chacun. Après un suivi moyen de 6,45±3,79 ans, six patients ont évolué vers l'insuffisance rénale terminale. Trois patients étaient décédés, tous suivis pour une hyperoxalurie primaire de type 1.

Conclusions : Les lithiases urinaires monogéniques, bien que rares sont très probablement sous diagnostiqués dans les pays où sévit une forte consanguinité comme la Tunisie. Le dépistage de ces maladies est primordial en raison de leur morbidité importante.

Mots-clés : Néphrolithiases, Hérédité, Pédiatrie, Gènes, Insuffisance rénale chronique, Pronostic, Tunisie.

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INTRODUCTION

Changes in dietary habits and the increasing frequency of metabolic syndrome have increased the incidence of urolithiasis worldwide [1]. However, in the pediatric population, the risk of developing urolithiasis remains 20 to 40 times less frequent [2]. Although rare, several recent studies report an increase in hospitalizations for lithiasis in children over the last two decades [3]. The discovery of urolithiasis in children should always lead to a careful etiological investigation to identify the underlying pathology. Hereditary diseases account for half of all lithiasis in children [4], these stones are more serious than stones secondary to urinary tract infection (UTI), urinary tract abnormalities or nutritional disorders. Several facts and/or clinical signs should alert to an underlying genetic disease in particular: parental consanguinity and family history of urinary stones.

Hereditary nephrolithiasis in children has been little studied in our country. Although it is a pathology that can lead to chronic kidney disease (CKD), to our knowledge, there are no recent studies that have focused on urinary lithiasis in children in Tunisia, their epidemiological profile, their etiologies and their nephrological outcome. The aim of this work was to study the etiological, genetic, epidemiological, and evolutive characteristics of monogenic urolithiasis in Tunisian pediatric patients during the period from January 1st 1996 to December 31, 2020 in the pediatric nephrology department in Charles Nicolle hospital, Tunis, Tunisia.

METHODS

This was a retrospective descriptive study over a 25-year period (January 1st, 1996 to December 31, 2020) conducted in the pediatric nephrology department of Charles Nicolle Hospital, Tunis, Tunisia which is considered as a referral center in the management of kidney disease in our country.

We included patients younger than 18 years at the time of diagnosis of the hereditary urolithiasis with or without nephrocalcinosis. Patients with urolithiasis of non-hereditary aetiology (secondary to UTI, malformative uropathy, or nutritional disorders), and those with nephrocalcinosis without associated lithiasis were excluded. The following items were recorded from the medical charts: Age at presentation, age at diagnosis of both urolithiasis and the underlying aetiology, consanguinity and family history of lithiasis, symptoms at presentation, time from symptom onset to diagnosis, results of the biological tests including blood and urine tests, treatment modalities and outcome.

Glomerular filtration rate (GFR) was calculated at the beginning of the follow-up and during the course of the disease using the revised Schwartz equation (2009) [5]. the Kidney Disease: Improving Global Outcomes classification was used to classify patients according to GFR and CKD stages [6].

The diagnosis of urolithiasis was made by the combined conventional radiography and renal ultrasound in the presence of a suggestive symptom or during the follow-up of the first pathological condition. The computed tomography was performed either to determine the density of the calculus, or for an obstructive calculus to evaluate the degree of obstruction. A dimercapto succinic acid renal scan was performed to evaluate the impact of the nephrolithiasis on the renal parenchyma.

24-h urine was collected in a plastic container with 20 ml 6 Molar HCl as a preservative from 6:00 a.m. to next day 6:00 a.m. either at home or as an inpatient. A volume of 10 ml of freshly voided spot urine was also collected from each patient to measure potential hydrogen. All patients were on a regular diet with no special instruction regarding diet and fluid intake. Patients who underwent intervention and 24-h urine samples were taken one month after complete stone clearance. Data were obtained and recorded in Excel sheet.

Genetic mutation analysis of hyperoxaluria, distal tubular acidosis and Lesch Nyhan disease was performed at the Genetic Department of Charles Nicolle Hospital in Tunis. The genetic assessment of the other diseases is currently not practiced in Tunisia and the diagnosis has been based on the clinical, radiological and biochemical arguments.

RESULTS

A total of 66 children were included in our study, the baseline characteristics of patients at diagnosis are summarized in Table 1. The inherited urolithiasis disorders found in our series were: primary hyperoxaluria (PH) in 44 cases, cystinuria in 9 cases, Lesch Nyhan syndrome in 5 cases. Renal tubular acidosis was found in 3 cases, and hereditary xanthinuria in 2 cases. Bartter syndrome, adenine phosphoribosyltransferase (APRT) deficiency and Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) were found in one case each.

Metabolic evaluation of urolithiasis was performed in 57 cases, it contributed to the etiological diagnosis of PH in 44 cases, distal tubular acidosis in 3 cases, APRT deficiency in 1 case, and Cystinuria in 9 cases (Table 2).

PH was the most common cause of monogenic urolithiasis in our series (66.66% of cases), the mean age at diagnosis was 5.92±3.6 years. In 23 patients, the diagnosis of PH type 1 (PH1) was confirmed by the first line of genetic tests. Five mutations were characterized: p.Ile244Thr, p.Gly190Arg, c.33dupC, p.Gln137Hisfs*19, and p.Arg360Gln. The most frequent mutation carried by our patients was the Ile244Thr with an allele frequency equal to 65.2%. The second most frequent mutation was p.Gly190Arg (allele frequency, 17.4). The mutations c.33dupC, p.Gln137Hisfs*19, and p.Arg360Gln were

found in two cases for the first one, and one case each for the last mentioned two. All patients were put on a diet low in oxalates, vitamin B6, magnesium sulphate and potassium citrate. Hyperhydration, potassium citrate, and magnesium were prescribed in patients without severe renal failure. Pyridoxine was prescribed in all cases. A double J-stent placement was performed in 3 cases because of an obstructive calculus. The treatment allowed a reduction of urinary oxalate in 59.5% of cases. Six patients progressed to end stage renal disease (ESRD). Seven patients progressed to stage 3 of CKD.

Table 1. Baseline characteristics of the 66 children with monogenic lithiasis follow up in the pediatric nephrology department at Charles Nicolle hospital, Tunis, Tunisia

Patient profile	n (%)
Categorical variables	
Male	35 (53)
Female	31 (47)
Male/Female ratio	1.12
Age of diagnosis according to age group	
- ≤ 2 Years	12 (18.18)
- 2-10 Years	45 (68.18)
- >10 Years	9 (13.63)
Age of diagnosis according to age group	
≤ 2 Years	17 (25.75)
1-1 Years	41 (62.12)
>10 Years	9 (13.63)
Consanguinity	40 (60.60)
Circumstances of UL diagnosis	
- Renal colic	34 (51.51)
- Family screening	8 (12.12)
- Hematuria	7 (10.60)
- Renal failure	6 (9.09)
- Urinary tract infection	5 (7.57)
- extra-renal signs	3 (4.54)
- Incidental findings	3 (4.54)
Stage of CKD	
- Stage 1	31 (46.96)
- Stage 2	22 (33.33)
- Stage 3	7 (10.60)
- Stage 4	4 (6.06)
- Stage 5	2 (3.03)
Quantitative variables	
Variables	**Mean±SD**
Mean age at diagnosis of the underlying disease	5.33±3.66 (range : 0 months-13.5 years)
Mean age at diagnosis of UL	5.92±3.48 (range: 4 months-13.5 years)
Mean weight (kg)	20.65±11.96
Mean height (cm)	107.32±26.44
Mean creatinine (µmol/l)	93.61±172.61
Time delay between the diagnosis of UL and the underlying disease (Years)	9.71±2.22

UL: *Urinary Lithiasis* ***CKD:*** *Chronic Kidney Disease*

Table 2. Biochemical characteristics of the 66 children with monogenic lithiasis follow up in the pediatric nephrology department at Charles Nicolle hospital, Tunis, Tunisia according to the aetiology of the urinary lithiasis

Biochemical parameters	Results
Primary Hyperoxaluria	**n=44**
- Monohydrate calcium oxalates de (Whewellite)	44 (100%)
- Cristal volume (µ3/mm3)	37527±1527
- Plasmatic oxalate (µmol/l)	10.4±6.7
- Urine oxalate (mmol/1,73 m2 SBA/day)	1.12±0.72
- Oxalate/creatinine ratio (mmol/mmol)	0.63±1.11
- Infrared spectroscopy	Type Ic
Cystinuria	**n=9**
- Colorimetric assay	9 (100%)
- Quantitative urinary amino acid chromatography (cystine/creatinine ratio)	1050±574 µmol/mmol
Lesch Nyhan syndrome	**n=5**
- Blood uric acid (µmol/l)	599.8±124.55
- Urinary uric acid (µmol/Kg/day)	600±247
Hereditary Xanthinuria	**n=2**
- Blood uric acid (µmol/l)	90 µmol/l
- Urinary uric acid (mmol/day)	1
- Xanthinuria (µmol/day)	1040.5
- Infrared stone composition	Xanthine (100%)
Distal tubular acidosis	**n=3**
- Urine pH	>6
- Citraturia (mmol/day)	<0.5 (100%)
- Metabolic acidosis	3(100%)
- Hypokalemia	3(100%)
- Hypercalciuria	3(100%)
APRT deficiency	**n=1**
- Urine microscopy	DHA crystals
- APRT enzyme activity in red cell lysates	Absent
Bartter syndrome	**n=1**
- Metabolic alkalosis	pH=7.52
- Calciuria	>4 mg/kg/day
Hereditary hypophosphatemic rickets with hypercalciuria	**n=1**
- Serum phosphate (mmol/l)	0.6
- %TRP	50%
- Calciuria	>4 mg/kg/day

APRT: *Adenine phosphoribosyltransferase* ***DHA:*** *Dihydroxyadenine* ***pH:*** *potential hydrogen* ***SBA:*** *surface body area* ***TRP:*** *Tubular reabsorption of phosphate*

Cystinuria was found in 9 cases (13.63%), the mean age at diagnosis was 5.86±4 years. Medical treatment (hyperhydration, urine alkalization, D-penicillamine) was prescribed in all patients. The diet was reviewed in all cases to avoid excessive protein and sodium intake while preserving the child's growth. Extracorporeal lithotripsy (ECL) was performed in 3 patients but was found ineffective in all these cases. A percutaneous nephrolithotomy was then performed with successful outcome.

Inborn errors of purine and pyrimidine metabolism were present in 8 cases (12.12%), they were dominated by Lesch Nyhan syndrome in 5 cases. The diagnosis of this disease preceded the diagnosis of urolithiasis in 4 out of 5 cases. These patients were put on Allopurinol,

with hyperhydration and urine alkalinization. Treatment allowed the reduction of uricemia from 599.8±124.55 µmol/l (range: 511-817 µmol/l) to 171±84.28 µmol/l (range: 120-318 µmol/l).

Xanthinuria was diagnosed in two children, a brother and his sister. The diagnosis followed a nephrectomy performed for the brother for an obstructive urolithiasis, and in the course of the investigation of a UTI with an index case for the sister.

APRT deficiency was diagnosed in a boy at the age of 18 months, an acute renal failure was the first clinical symptom.

Hereditary tubulopathies were found in 5 cases: distal tubular acidosis was found in three cases, Bartter's syndrome in one case, and HHRH was the cause of urolithiasis in one case.

The outcome of the patients was characterized by the occurrence of ESRD in 6 cases. Three patients died; they were followed for PH on hemodialysis. The age at death was 18 years in two cases and 10 years in the third case.

DISCUSSION

We found that hereditary nephrolithiasis was as frequent in boys as in girls. The age of diagnosis of the lithiasis and the underlying pathology was approximately the same. The main pathology was PH and the most frequent diagnostic circumstance was renal colic. Progression to chronic renal failure with a creatinine clearance of less than 60 ml/1.73m2BA was found in 18 cases.

The incidence of urolithiasis is increasing in both children and adults [7-8], the frequency of hereditary urolithiasis is estimated at about 1 to 2% of stones in adults and 5 to 10% of those in children. However, their real frequency is probably underestimated because many cases are not well known. The diagnosis age varies from one series to another and depends on the underlying pathologies. The average age at the time of onset of the underlying disease was 20.6 years (3 months-59 years) and the average age at the time of diagnosis of the hereditary cause was 28.6 years (3 months-63 years) according to Kaaroud et al [9]. The average age of diagnosis was 4 years (range: 5 months-14 years), and 11.5 years (range: 6-15.5 years) in other pediatric series [10-11].

A male predominance has been reported in most series of monogenic urolithiasis in children. In our series the sex-ratio was 1.12, it was 1.19, 1.4, 2.29 and 1.55 for Medairos et al, Kaaroud et al, Ge et al and Amar et al [11,9,7,12].

Consanguinity was found in 53.8% of cases in the series of Kamoun et al [13], and in 94% in the series of Kaaroud et al [9]. Consanguinity is a determining factor in hereditary lithiasis according to Cogal et al [14]. It was found in 60.6% of cases in our series.

The main cause of urolithiasis in our series was PH, the disease is more frequent in countries with high consanguinity [15]. The p.Ile244Thr mutation was the most common mutation in our patients (15/44). This mutation has always been described as the main cause of PH1 in Tunisia and in the Maghreb countries, it is associated with a founder effect [16-19]. The predominance of this mutation in the Tunisian population has been reported by all Tunisian series. M'dimegh et al reported a frequency of 43.4% [20]. The most common mutation in the European and American populations is p.Gly170Arg (G170R) [21-23]

All our patients were put on hyperhydration, diet low in oxalates, pyridoxine, potassium citrate if renal function allows it and in magnesium sulphate. Minimally invasive urological treatment such as Stone Flexible Laser Ureteroscopy deserves to be tried during obstructive urolithiasis. Extracorporeal ECL and other invasive methods can precipitate progression to ESRD due to the parenchymal lesions and oxidative stress they can cause [24-27].

Cystinuria is the cause of about 10% of urinary stones in children between 10 and 15 years old [28], it was present in 13.63% of our patients. Its overall prevalence is 1/7000 on average but it varies considerably between countries [29,30]. The cyanide-nitroprusside reaction, developed by Brand et al. in 1930, provided a qualitative method of measuring excessive urinary excretion of cystine [31]. It must be combined with a urinary amino acid chromatography [31]. The medical treatment was started in all our patients, it was based on hyperhydration, a low sodium and relatively low animal protein diet, urine alkalinization and D-penicillamine prescription. Surgical treatment is based on ureteroscopy, percutaneous nephrostomy. ECL keeps its indications despite its low efficiency.

Five children with urolithiasis had Lesch Nyhan syndrome. A complete Hypoxanthine Guanine Phosphoribosyl Transferase deficiency results in Lesch-Nyhan syndrome characterized by massive overproduction of Uric acid responsible for major hyperuricemia and hyperuricuria with early tophaceous gout, bilateral uric lithiasis and crystal infiltration of the renal parenchyma, associated with severe neuropsychological impairment that appears from the first year of life [32]. The neurological involvement in Lesch Nyhan syndrome was present in all our patients. In Tunisia, the actual frequency of the disease is unknown, it is estimated at 1/380000 births in Canada and 1/235000 in Spain [32]. Molecular diagnosis allows the identification of transmitter subjects as well as prenatal diagnosis [33,34]. The treatment is based on Allopurinol, it has no influence on the neurological signs which require palliative treatment with neuromodulators and protective measures against self-mutilation of the fingers and lips [34,35].

Hereditary Xanthinuria was found in only two of our patients, it is a rare disease, transmitted according to the autosomal recessive mode, characterized by the deficiency of xanthine oxidase, or xanthine dehydrogenase activity [36]. Hypouricemia most often reveals the disease, which can also cause arthralgia, myalgia or duodenal ulcer due to the deposition of xanthine crystals in different tissues [37]. The disease is mostly benign and rarely results in ESRD.

APRT deficiency, which is inherited in an autosomal recessive pattern, causes the accumulation of 2,8-dihydroxyadenine (2,8-DHA), a highly insoluble metabolite, leading to stone formation and crystal infiltration in the renal parenchyma, which frequently leads to ESRD. [38]. In our series, inaugural acute renal failure allowed the diagnosis of urolithiasis in an 18-month-old infant. The treatment is based on Allopurinol, associated with the maintenance of hyperhydration and the reduction of purine intake. The total or at least significant disappearance of 2,8-DHA crystals on regular monitoring of crystalluria is the best indicator of compliance and effectiveness of the treatment [39]. The outcome under treatment in our patient was favorable.

Inherited tubulopathies leading to urolithiasis in our series were dominated by distal tubular acidosis, the association of biological abnormalities and nephrocalcinosis quickly leads to the diagnosis in these cases [40]. HHRH is an autosomal recessive disease, it is caused by a mutation in the SLC34A3 gene encoding the co-transporter NPT2c [41-42]. It results in rickets, growth retardation, renal leakage of phosphates and hypercalciuria resulting from production stimulation of calcitriol as a reaction to hypophosphatemia, with in some cases urinary lithiasis and nephrocalcinosis [42]. Vitamin D deficiency may mask hypercalciuria [43].

To the best of our knowledge, this is the first Tunisian study to focus on hereditary urinary lithiasis in the pediatric population. However, its limitation remains its monocentric and retrospective approach with some missing data.

Because of their rarity, monogenic lithiasis diseases can be diagnosed late. This delay in diagnosis is prejudicial, as it deprives young patients of the specific treatment that is the only option to prevent or at least substantially delay the onset of end-stage renal disease, if started early.

According to our results, PH is the first cause of monogenic urinary lithiasis in children. The severity of this pathology incites us to its early detection especially in the regions of the country known to be endemic of this disease and in families at risk to avoid the deterioration of the renal function and the evolution towards CKD. Also, we insist on the importance of genetic study and prenatal diagnosis which will allow us to anticipate, to make an early diagnosis and a fast management. We also think that this work could incite to practice a multicentric study to better discern the profile of children with hereditary urolithiasis.

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