

Paediatric nephrolithiasis and nephrocalcinosis: a 20 year retrospective analysis

Sofia A. Martins, Clara Gomes, A. Jorge Correia

Nephrology Unit. Hospital Pediátrico de Coimbra. Coimbra, Portugal.

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■ ABSTRACT

Aims: Nephrolithiasis and nephrocalcinosis are progressive diseases that can lead to renal impairment. The aim of this analysis was to evaluate aetiological factors, metabolic screening, diagnostic algorithm, treatment, prophylactic measures and follow-up in children with nephrolithiasis and nephrocalcinosis.

Patients and methods: Retrospective study of 63 children (36 males, 27 females) with nephrolithiasis and/or nephrocalcinosis followed up in the Paediatric Nephrology Unit of Coimbra Paediatric Hospital during a period of 20 years. The parameters analysed were gender, age at diagnosis, year of diagnosis, calculi site, metabolic factors, urinary tract abnormalities, treatment, follow-up, personal history of urinary tract infections (UTI) and family history of nephrolithiasis. All children underwent a metabolic screening that included plasma biochemistry evaluation, blood gas analysis and 24 hour urine collection for assessment of lithogenic factors. All the data and statistical analysis were handled using SPSS 10.

Results: We detected 46 cases of nephrolithiasis, 15 of nephrocalcinosis and 2 of nephrolithiasis and nephrocalcinosis. The median age at diagnosis was 6 years for nephrolithiasis (1-16) and 1.4 years for nephrocalcinosis (0.1-14), 48 (76%) of the cases were diagnosed in the last ten years. In 19 (30%) of the children the diagnosis was made following UTI and in 10 (16%) following an episode of renal colic. Fam-

ily history of nephrolithiasis was found in 25 cases (40%). Eight children (13%) had abdominal X-rays and all underwent ultrasonography. Eighty five percent of the calculi were found in the kidneys, 13% in the ureters and 2% in the bladder. Nephrocalcinosis was bilateral in 100% of the cases. The main aetiological factors were UTI (30%), urinary tract abnormalities (22%), tubular renal acidosis (14%) and hypercalciuria (11%). During follow-up, 21 (33%) were discharged calculi free and 7 (11%) were transferred to adult hospitals.

Conclusions: Investigating and treating UTI is necessary to prevent subsequent renal impairment. Equally so, metabolic and structural abnormalities that predispose to nephrocalcinosis and nephrolithiasis should be investigated and treated.

■ Key-Words:

Calculi; children; nephrocalcinosis; nephrolithiasis; urinary tract infection.

■ INTRODUCTION

The presence of calculi in the urinary tract is referred to as nephrolithiasis. It has a multifactorial aetiology involving genetic, environmental, racial and structural factors^{1,2}. The incidence in children is 2-3%³. In Europe the main cause is infectious agents⁴ (*proteus mirabilis*, *klebsiella*). Calculi are usually located in the upper urinary tract and are mainly made up of struvite (calcium phos-

phate, ammonium and magnesium)⁴. The major metabolic cause is hypercalciuria. In the USA, nephrolithiasis is rare and its aetiology is mainly related to metabolic disorders: hypercalciuria, distal tubular renal acidosis (DTRA), cystinuria, and purine metabolism disturbance. Nephrocalcinosis refers to the amount of calcium found in the kidney, frequently caused by hypercalciuria, DRTA and hyperoxaluria. In these situations it is usually medullary, but it can be cortical (focal), usually related to previously damaged parenchyma⁴. Both can progress to chronic renal impairment if not correctly investigated and treated.

Our aim was to evaluate the aetiological factors involved, review prophylactic measures, assess diagnostic methodology and management and update the protocol used since 1985 in the light of the latest advances in knowledge.

PATIENTS AND METHODS

This was a retrospective study of 63 children with nephrolithiasis/nephrocalcinosis followed up at the Paediatric Nephrology Unit of Coimbra Paediatric Hospital over a period of 20 years. The parameters evaluated were gender, age at diagnosis, year of diagnosis, calculi site, metabolic factors and structural abnormalities of the urinary tract, treatment and follow up and personal and family history of renal disease. The analytical study included urea and electrolytes, total protein, full blood count, blood gas analysis and 24h urine collection for creatinine, proteins, calcium, uric acid, magnesium, oxalate, phosphate, cystine and citrate measurement (Table I).

Table I

Cut off of 24 hours urine lithogenic factors used in our Nephrology Unit.

	24 h urine normal values
Calcium	< 4 mg/kg/24h
Uric acid	< 815 mg/1.73m ² /24h
Magnesium	> 88 mg/ 1.73 m ² / 24h
Oxalate	< 50 mg/1.73m ² /24h
Cystine	Heterozygote 1.4-2.8 mg/kg/24h Homozygote > 5.7 mg/kg/24h
Citrate	> 150 mg/24h

RESULTS

Thirty six of the 63 children were male (57%), two non-Caucasian. There were 46 cases of nephrolithiasis, 15 cases of nephrocalcinosis and 2 with both nephrolithiasis and nephrocalcinosis. The majority 48 (76%) were diagnosed in the last 10 years. The median age at diagnosis was 6 years for nephrolithiasis (1-16) and 1.4 years for nephrocalcinosis (0.1-14). The mean follow-up was 4.3 ± 3.8 years.

The causes that led to diagnosis were 19 UTI (30%), 10 renal colic (16%), 7 failure to thrive (11%), 7 urinary tract symptoms (11%), 6 abdominal pain (9.5%), 5 haematuria (8%) and 9 miscellaneous (14%). Eight children (13%) had abdominal x-rays and radiopaque calculi were found in 5 children. All children had abdominal ultrasonography. The calculi were unilateral in 70% of the cases. 85% were located in the kidney (Fig. 1), 13% in the ureters and 2% in the bladder (Fig. 2). Nephrocalcinosis was always bilateral and medullary. Structural/functional abnormalities of the urinary tract were present in 14 children (22%): 8 with hydronephrosis, 4 with vesical dysfunction, 1 with posterior urethral valves and 1 with vesico-ureteral reflux. Past history of recurrent UTI was found in 12 children (19%) with six (9.5%) having only one UTI. Three children had repeated *proteus* infections. One child was being treated chronically with frusemide and one case was related to excessive vitamin D intake. None of these children was born preterm. Four children had

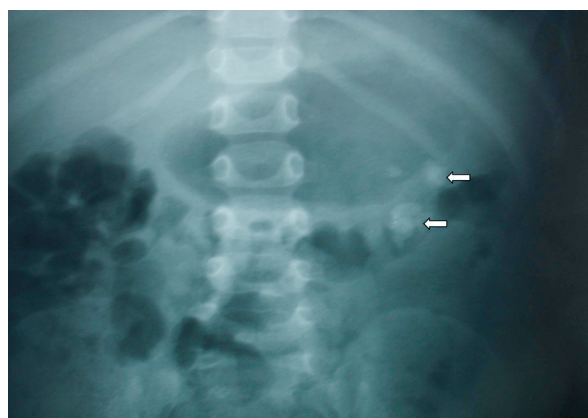


Figure 1

The plain abdominal x-ray shows multiple left renal calculi



Figure 2

Plain abdominal x-ray: bladder calculi detected after the investigation of a UTI

associated haematological disorders, namely sickle cell disease, spherocytosis, haemophilia and high affinity haemoglobin. One had Beckwith-Wiedman syndrome with neuroblastoma. In addition, hypothyroidism and excessive milk intake (3 L/day) were detected in 2 separate children. There was family history of lithiasis in 25 cases (40%).

The urine analysis and serum and urine biochemistry were performed in line with current protocol algorithms. Several metabolic disturbances were found (Table II).

Calculi composition was possible in 14/63 (22%) cases: 5 were struvite, 5 calcium oxalate, 2 cystine and 2 calcium phosphate calculi.

Table II

Nephrolithiasis primary risk factors found in our patients

DTRA	9
Idiopathic hypercalciuria	7
Hyperuricosuria	3
Lesch Nyhan disease	1
Cystinuria	3
Glycogenosis	1
Hypomagnesiuria	9
Hypomagnesiuria + hypercalciuria	4
Hyperoxaluria	3
Hypocitraturia (without DTRA)	9

A comparative analysis of nephrolithiasis and nephrocalcinosis was performed in terms of age at diagnosis, gender, risk factors and follow-up (Tables III and IV).

Table III

Comparative analysis of nephrolithiasis and nephrocalcinosis in our patients

	Nephrolithiasis	Nephrocalcinosis	Nephrolithiasis + Nephrocalcinosis
Number	46	15	2
Age (years) (median, minimum-maximum)	6 (1-16)	1.4 (0.1-14)	1.8 (1.3-3)
Gender (Male/Female)	29/17	5/10	2/-
Main aetiopathogenic factors			
UTI	16	2	–
Anatomic/functional abnormalities	10	4	–
Metabolic abnormalities	37	10 (DTRA 7)	(DTRA)
Follow-up			
Decreased GFR	–	1	1
HTA	1	–	–

Table IV

Risk factors of nephrolithiasis and nephrocalcinosis

	Nephrolithiasis	Nephrocalcinosis	Nephrolithiasis + Nephrocalcinosis
One single risk factor (38)			
UTI (single or recurrent)	8	2	–
Anatomic/functional abnormalities	3	2	–
DTRA	–	6	2
Other metabolic abnormalities	15	–	–
Two risk factors (19)			
Metabolic abnormalities	8	–	–
Anatomic/functional abnormalities	1	1	–
Metabolic+Anatomic/functional abnormalities	3	1	–
UTI+Metabolic abnormalities	2	1	–
UTI+ Anatomic/functional abnormalities	2	–	–
Three or more risk factors (4)			
Metabolic abnormalities	1	–	–
UTI+ Anatomic/functional abnormalities	1	–	–
UTI+ Metabolic abnormalities	1	–	–
UTI+ Anatomic/functional abnormalities + metabolic abnormalities	1	–	–

Treatment was related to the underlying cause identified. Antibiotics and later prophylaxis for recurrent UTI were given in 6 (9.5%). Ten children (16%) (9 with DTRA and 1 with Lesch-Nyhan disease) began supplementation with bicarbonate or Shohl's solution, allopurinol (Lesch-Nyhan disease) and captopril (cystinuria). In the hypercalciuria/hyperoxaluria cases milk based products were restricted. Every child was encouraged to increase water and fibre intake.

Spontaneous elimination of calculi was observed in 8 children and in 3 the calculi were larger than 5 mm in diameter (6, 10 and 11 mm). Eleven children (17.5%) were managed surgically (nephrolithotomy, pielolithotomy, ureterolithotomy, cystostomy) and 4 with shock wave lithotripsy (SWL).

During follow up (n=63), 46 (73%) children improved, 1 worsened and in 7 (11%) calculi recurrence was evident. Recent (less than 6 months) urinary tract signs or symptoms such as abdominal pain and dysuria were present in 16 children (25%). Serum creatinine was raised in 3 adolescents (DTRA, posterior urethral valves and Lesch Nyhan disease). Glomerular filtration rate of about 70 ml/min/1.73 m² was found in 2 children and one child is on anti hypertensive therapy (Lesch Nyhan disease).

At the last evaluation, 35 (55.5%) children are still being followed up, 21 (33%) had been discharged and 7 (11%) with lithiasis transferred to adult hospitals.

DISCUSSION

Nephrolithiasis affects both genders equally¹, with a peak incidence at 4 years of age³. In our series there was a slight male predominance and the median age at diagnosis was 6 years. Nephrolithiasis is usually suspected in the context of recurrent UTI, renal

colic episodes, haematuria, the presence of urinary calculi or its fragments and rarely acute renal failure^{1,3,4}. Renal colic is the most frequent symptom in adults, whereas in children the main complaint is usually abdominal or pelvic pain^{1,4}. Microscopic haematuria is found in about 90% of children with calculi^{1,4}. Nephrocalcinosis is usually asymptomatic, but polyuria can be present. In our series failure to thrive led to diagnosis in 7 cases and polyuria in 3 cases. The age of diagnosis was lower (1.4 years) and there was a clear female predominance.

The past ten years have seen a significant increase in the diagnosis of these pathologies, which the authors relate to a greater awareness and broader investigation of all suspected UTI. This included submitting all patients to renal US. Others causes cited in the literature that might be related to this increase are dietary habits high in lactic products, sodium and protein content⁵.

The pathways involved in calculus formation are, as yet, not completely understood. It is known that future calculi will most likely develop when urine is fully saturated with a specific component. The thermodynamic stress that is needed for the crystallisation of these components can be modified by promoting or inhibiting factors^{2,4} (Table V). Structural abnormalities and urinary stasis promote crystal retention and its nucleation and aggregation leads to final calculi formation.

A metabolic and anatomical investigation should be made of every child with nephrolithiasis. There were structural abnormalities in almost a quarter (22%) of our cases and in 36.5% there were two or more risk factors. Alkaline urinary pH >5.5, usually found in UTI, DTRA and primary hyperparathyroidism, promotes precipitation of calcium phosphate, ammonium and magnesium phosphate crystals². Acid urinary pH <5.5 promotes the precipitation of uric acid

Table V

Some inhibiting and promoting factors for the development of urinary calculi

Inhibit the calculi growth and aggregation: Glicosaminoglicans, Nephrocalcin, Uropontin, renal lithostatin, bikunin, crystal matrix protein	Accelerate the calculi growth and aggregation: Mucoproteins, Uromucoid
Decrease urinary saturation, forming more soluble associations: Citrate + Calcium Magnesium + Oxalate	Increase urinary saturation of lithogenic compounds: Hypercalciuria, Hyperuricosuria, Hyperoxaluria, Cystinuria

and cystine crystals; hence the importance of urine alkalinisation in cystinuria⁶ and purine disorders².

The most important aetiological factors were UTI (30%) and structural abnormalities of the urinary tract (22%). DTRA and hypercalciuria were the major metabolic disturbances found in our series, in line with findings described in current medical literature⁴. Recurrent UTI were observed in 12 children. The association between UTI and *proteus* should always prompt the physician to look for nephrolithiasis, particularly in antibiotic resistant infections^{1,4}. In 85% of the cases caused by an infectious agent, the calculi are mainly found in the renal pelvis, are made up of struvite (magnesium and ammonium phosphate crystals) and most adopt the shape of the renal pelvis (staghorn calculi)^{1,4}.

Urinary calculi can be classified based on their radiological opacity (Table VI). Nephrocalcinosis is less obvious in x-ray examinations, but US is a sensitive exam⁷ (Fig. 3). In our series all the children underwent renal US, but only 8 (13%) had plain abdominal x-rays. This exam should be performed initially in all children as the majority of the calculi are radiopaque¹ and other calculi must be searched for in the whole urinary tract.

Table VI

Calculi composition and appearance in abdominal plain x- rays

Radiopaque Calculi	Radiotransparent Calculi
Struvite	
Calcium oxalate	Uric acid
Calcium	Xantinuria
Oxalate	Orotic aciduria
Cystine	

Calculi elimination was seen in 8 children and in 3 of these, the calculi were larger than 5 mm, despite the 5mm limit described for spontaneous elimination⁸. As analysis of calculus is important, both parents and child should be aware of the importance of keeping it. SWL is the ideal treatment for calculi smaller than 2 cm and located in the renal pelvis and superior ureter^{2,8,9}. Those greater than 2-3 cm in diameter usually require open surgery or percutaneous nephrolithotomy, as do staghorn and cystine calculi. Four children underwent SWL and 11 surgical therapy (nephrolithotomy, pielolithotomy, ureterolithotomy and cystostomy).



Figure 3

US showing nephrocalcinosis in a 4 month old boy

Recurrent nephrolithiasis and its complications are the only clinical signs of cystinuria and can be avoided or minimised by prescribing the correct treatment⁶. The exclusion of this condition is crucial. Brandt's reaction is referred to as a simple exclusion test, but in our series was always negative even in the confirmed cystinuria cases.

As urinary citrate is an inhibitor of uric acid and calcium salts crystallisation and low urinary magnesium is also a promoter of calcium calculi, their intake form part of the management strategy¹. Ten children began oral supplementation with bicarbonate or Shohl's solution.

During follow-up recurrent nephrolithiasis was found in 13% of our cases. One third were discharged (33%) and 7 transferred to adult hospitals. Because of the high relapse rates (up to 67%)^{3,10}, regular observation of these children is advised.

CONCLUSIONS

A detailed clinical history and physical examination should be part of the work-up in a child with suspected nephrolithiasis/nephrocalcinosis. Personal and family history of renal problems, particularly

UTI and lithiasis, should be investigated^{1,2}. Multifactorial causes of nephrolithiasis often coexist in the same child. Investigation should include systematic urine analysis, structural abnormalities and metabolic disturbances screening, the latter with the patient on a regular diet². Abdominal plain x-rays should be the initial imaging in all children, as the majority of the calculi are radiopaque.

Isolated idiopathic hypercalciuria, DRTA and hypomagnesiuria were the most frequently found disorders. Management of nephrolithiasis/nephrocalcinosis in children should include calculus removal and avoidance of its reoccurrence. As such, the adequate treatment/prophylaxis of UTI and the structural and metabolic abnormalities are of the utmost importance. This management strategy should always involve a multidisciplinary team whose aim is the prevention of further renal impairment.

Conflict of interest statement. None declared.

References

- ¹ Gillespie R, Stapleton FB. Nephrolithiasis in children. *Pediatrics in Review* 2004; 25:131-139.
- ² Trapote RA, Garagorri MU, Arrieta MU, Monge T, Lizarraga D. Evaluación de la enfermedad renal litiasica. Estudio metabólico. *An Pediatr (Barc)* 2004;61: 418-427.

- ³ Erbagci A, Erbagci AB, Yilmaz M *et al.* Pediatric Urolithiasis, Evaluation of risk factors in 95 children. *Scand J Urol Nephrol* 2003;37:129-133.
- ⁴ Hulton S. Evaluation of urinary tract calculi in children; *Arch Dis Child, Grupo Aula Médica SA*; 2000:461-473.
- ⁵ López AH, López-Mencheró JC, Gutiérrez C *et al.* Nefroureterolitiasis en niños: revisión de los últimos cinco años. *Rev Port Nefrol Hipert* 2005;19:149-154.
- ⁶ Knoll T, Zollner A, Wendt-Nordahl G, Michel M, Peter Alken. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment and follow-up. *Pediatr Nephrol* 2005;20:19-24.
- ⁷ Agraharkar M, Gupta R, Sealy J. Nephrocalcinosis. Published online in e-medicine 2002.
- ⁸ Pietrow P, Pope J. IV, Adams M, Shyr Yu, Brock J. Clinical outcome of paediatric stone disease. *J Urol* 2002;167:670-673.
- ⁹ Braun PM, Seif C, Junemann K, Alken P. Urolithiasis in children. *Inter Braz J Urol* 2002; 28:539-544.
- ¹⁰ Ali SH, Rifat UN. Etiological and clinical patterns of childhood urolithiasis in Iraq. *Pediatr Nephrol* 2005;20:1453-1457.

Correspondence to:

Dr Sofia A. Martins
Unidade de Nefrologia, Hospital Pediátrico de Coimbra.
Avenida Bissaya Barreto
3000-076 Coimbra
Portugal