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Chronic Tubulointerstitial Nephropathies (CTIN) in Children in the Paediatric Nephrology Department of Dakar: About 64 Cases between January 2015 and December 2022

Keita Y[1,2], Faye M[1,2], Dione S[2], Ndongo AA[1,2], Faye AA2, Sow A[1,3], Boiro D[1,3], Faye M[1,2], Bacary BA[1,2], Seye MD[3], Takam BL[3], Seck N[4], Abou BA[1,5], Indou Deme LY[1,6], Thiongane A[1,6], Fatou LY[1,7], Lemrabott AT[1,2], Gueye M[1,3] and Sylla A[1,2]

[1C]*heikh Anta Diop University of Dakar, Senegal*
[2]*Aristide Le Dantec University Hospital of Dakar, Senegal*
[3]*Abass Ndao university hospital of Dakar, Senegal*
[4]*Gaston Berger University of Saint-Louis, Senegal*
[5]*Dalal Jamm Hospital of Guédiawaye, Senegal*
[6]*Albert Royer university hospital of Dakar, Senegal*
[7]*Pikine university hospital of Dakar, Senegal*

[*]**Corresponding author:** Keita Y, Pediatric nephrologist, ISN past fellow, Aristide Le Dantec Hospital (HALD), Cheikh Anta Diop university, Dakar, Senegal; E-mail: younouss_keith@yahoo.fr

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Abstract

Objective: To describe the diagnostic, therapeutic and evolutionary aspects of the CTIN cases treated in our department.

Patients and Method: We conducted a descriptive and analytical retrospective study of CTIN cases treated in the only paediatric nephrology department in Senegal between January 2015 and December 2022. The data collected were analysed with SPSS version 21 software.

Results: After data collection, 64 children were included during the study period, corresponding to a hospital prevalence of 9% (64/709) of the chronic kidney disease (CKD) monitored in our department. The average age of the children at the onset of the disease was 5.5 ± 5.3 years. The gender ratio (M/F) was 2.4 (45/19). The reasons for consultation were lumbar pain 28.1% (18/64), hypertension 17.2% (11/64), fever 15.6% (10/64), polyuropolydipsia 12.5% (8/64), proteinuria 12.5% (n=8), abacterial leukocyturia 6.2% (4/64) and hematuria 3% (2/64). Ultrasound examination revealed nephrocalcinosis in 43.9% (28/64) of cases. A renal biopsy was performed in 6.2% (4/64) of patients, confirming typical CTIN lesions. Crystalluria testing identified revealed uric acid in one case and a cystine calculus in another. Genetic testing was performed in 4.6% (3/64) of the children with 01 claudin-16 mutation, and 02 cases of familial mutation of the CTNS gene. Hereditary tubulopathies accounted for 53.1% (34/64) of the causes of CTINs, followed by reflux nephropathy 18.8% (12/64). The hospital mortality rate was 6.2% (4/64). Death was related to the development of CKD to dialysis stage V (p=0,001).

Conclusion: In our study, CTINs accounted for less than one tenth of the causes of CKD in children. Limited access to genetics and specific blood and urine tests was the major limitation in this study. Therefore, there is a need to provide diagnostic tools for CTIN in Dakar.

Keywords: Polyuria-polydipsia; Nephronophthisis; Nephrocalcinosis; Tubulopathies; Chronic kidney disease

Introduction

Chronic tubulointerstitial nephropathy (CTIN) is a large and heterogeneous group of nephropathy that predominantly or

exclusively affects the renal interstitium and takes longer than three months to develop [1-3]. Regardless of the cause, the majority of renal damage leads to the development of interstitial fibrosis and tubular atrophy, the presence of which indicates the inevitable progression to loss of renal function [1]. The phenotypic manifestations of CTINs are often diverse and are described as less specific [4]. Diagnostic certainty is based on renal biopsy [5]. However, in most studies, histological confirmation of CTIN cases is not always effective and the diagnosis relies on a number of presumptive arguments. In renal pathology, tubulopathies are less common than glomerular diseases [6]. Little is known about the prevalence of CTINs in children in sub-Saharan Africa, so our research hypothesis was that CTINs are common in children in Dakar and that there are several different aetiologies. The present study was conducted in this context with the aim of investigating the epidemiological, clinical, and paraclinical profile as well as the diagnosis of CTINs in children in the only paediatric nephrology department of Dakar.

Patients and Method

The study was conducted in Senegal's only paediatric nephrology department at Aristide Le Dantec University Hospital. Paediatric nephrology activities in this department included outpatient consultation, hospitalisation, renal biopsy and dialysis. In most cases, the children to be treated were referred by the pediatric facilities in Dakar and other regions of the country. Biological and radiological tests were available in Senegal, with the exception of genetics, some specific dosages, and immunofluorescence and urodynamic tests. Only a few families were able to access all the tests required for each case. Kidney transplant has been authorised in Senegal since 2015, but was not yet effective at the time of our study. We conducted a descriptive and analytical retrospective study over the period from January 2015 to December 2022. All cases of CTIN in children under 16 years of age were included in the study. CTIN was considered in patients with suggestive clinico-biological and radiological syndromes and/or lesions of interstitial fibrosis and tubular atrophy in renal biopsy with or without genetic addition. The aetiology was determined on the basis of the disease phenotype in most cases by comparing the clinical and paraclinical data recorded in a specific questionnaire. The case was excluded if the diagnosis of CTIN could not be established. Data were entered using Epi info version 7 and analysed using SPSS version 21. In the descriptive analysis, the qualitative variables were expressed as number and percentage and the quantitative variables as average with standard deviation, extreme values and median. In the analytical study, the incidence of end stage renal failure and death were compared by variable. The statistical tests used were the Khi2 or Fisher test for percentage comparison and the Student t test for average comparison. The difference was statistically significant if the p-value was strictly less than 0.05.

Results

At the end of the survey, 64 cases of CTIN were recorded in 709 children with chronic kidney disease. The hospital prevalence was 9% (64/709), which corresponds to an average of 08 cases per year in the department. The average age of children at onset of symptoms was 5.5 ± 5.3 years with a median age of 4 years and extremes of 0 and 15 years. The average age at admission to paediatric nephrology was 6.4 ± 4.4 years with a median of 5 years, corresponding to an average diagnostic pathway of 1 year? The gender ratio (M/F) was 2.4 (45/19). 73.4% (47/64) of the children were coming from Dakar region. Consanguinity was found in 11% (7/64) of cases. The reasons for consultation as well as biological blood and urine findings are listed (Tables 1,2).
Bacteriological examination of urine was positive in 11% (7/64) of cases and detected Escherichia coli in 42.8% (3/7) of cases. Ultrasound examination revealed nephrocalcinosis was present in 28.1% (18/64) of cases, urinary tract malformation in 17.2% (11/64) of cases, and an obstructive intra-bladder stone in an uroscanner- confirmed case (Figure 1).

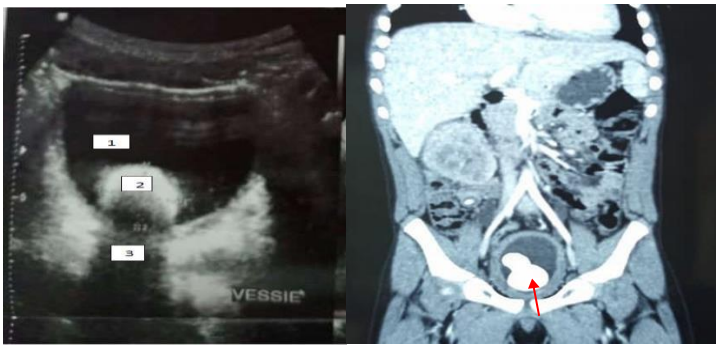

Figure 1: *Ultrasound axial and sagittal section showing urosacnner-confirmed nephrolithiasis in a child with cystinuria: 1. Bladder, 2. Scan-confirmed lithiasis (red arrow), 3. Posterior shadow cone.*

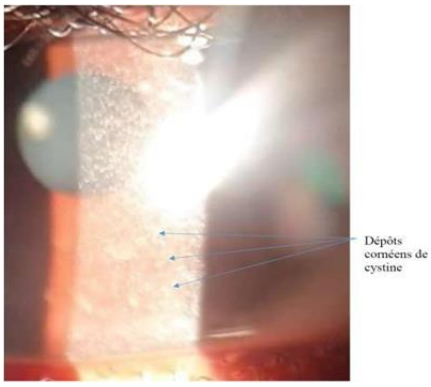

Figure 2: *Corneal cystine deposits (blue arrows) in a child with cystinosis*

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Two children showed a cystine deposit on the cornea in an ophthalmologic slit-lamp examination (Figure 2). Crystalluria examination revealed 01 case of uric acid and 01 other case of cystine calculi. Renal biopsy confirmed mutilating interstitial fibrosis with glomerulosclerosis and tubular atrophy in 4 children during nephronophthisis (Figure 3).

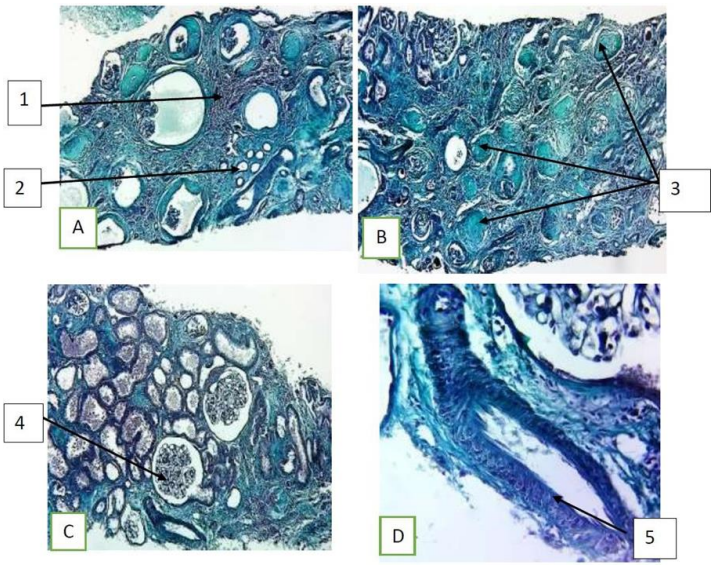

Figure 3: *CTIN in a 13-year-old polyuric patient with nephronophthisis. A. Interstitial fibrosis, tubular atrophy and mononuclear interstitial leukocyte infiltrate, 1A. Interstitial fibrosis, 2A. Tubular atrophy; B. Diffuse glomerulosclerosis, 3B. Sealing-bread glomerulus; C. Nephronic compensatory hypertrophy, 4C. Glomerular hypertrophy; D. Artery with slight atherosclerosis; 5D. Atherosclerosis. Optical microscopy Masson's Trichome x 200.*

In the genetic study, two brothers were found to have a family mutation of the CTNS gene, which codes for cystinosin, and in 01 case a mutation of claudin 16. Aetiologically, hereditary CTINs accounted for 53.1% (34/64) and reflux nephropathy 18.8% (12/64) of cases. All identified causes are listed in (Table 3). Chronic kidney failure was found in 62.5% (40/64) and correlated with proteinuria (p=0.034) and anaemia (p=0.003). Therapeutically, symptomatic treatment and dietary health measures were suggested in 90.6% (58/64) of cases. Dialysis was performed in 12.5% (8/64), of which 75% (6/8) underwent hemodialysis. Bladder calculi in cystinuria and malformative uropathies were treated paediatric surgery. Mortality in hospitalized patients was 6.25% (4/64) of cases. Death correlated with late initiation of dialysis if indicated (p=0,001).

Discussion

The prevalence of CTINs in children in sub-Saharan Africa is not well known. In our study, it was estimated to be 9% of children's chronic kidney disease. In a previous study conducted in Senegal, Keita and al. reported a prevalence of 12% [7]. This result is confirmed by the work of Ramilitiana and al. in Madagascar, who found a prevalence of 10.46% [8] and by the study of biopsy is not routinely performed in a suspected case of CTIN, as in the study by Fongoro et al in adults in Mali [10]. The lack of routine renal biopsy may lead to under- or overestimation of the prevalence of CTINs. In addition, specific blood and urine tests, dynamic tests as well as genetic testing are not always available in most sub-Saharan African countries, which was the case in Senegal at the time of the study. The lack of national nephrology registries, the shortage of nephrologists in general and paediatric nephrologists in particular in our sub-region are all factors limiting CTIN knowledge in sub-Saharan Africa. The average age of children at onset of the disease was 5.5 ± 5.3 years with a 1-year delay in diagnosis. This delay in diagnosis could be due to ignorance of the very non- specific symptoms as well as the lack of paediatric nephrology specialists in the country. In the study by Murray et al [11], a male predominance was found. This male predominance may be explained by the high incidence of reflux nephropathy in boys. The manifestations of CTINs are diverse and non-specific and often include polyuropolydipsia, stunting, and high blood pressure (HBP) in advanced CKD [4]. In our work, polyuropolydipsia, HBP, stunting and extrarenal signs were reported. Polyuropolydipsia is often caused by a lack of urine concentration involving hormones such as ADH and Aldosterone. Stunting is often related to the severity of tubulopathy, but also to chronic metabolic acidosis [12]. According to Glovis et al, HBP is rare in CTINs [5]. Other manifestations of tubulopathies may be extrarenal, in particular ophthalmological, osteoarticular, dental, neurosensory and psychomotor skills acquisition disorders [13,14].

Paraclinically, hypercalciuria, nephrocalcinosis, nephrolithiasis, hypo or hyperkalemia and disorders of calcium and phosphate metabolism, blood gas disorders in tubulopathies are common [4]. The investigations are therefore numerous, varied and sometimes specific: blood biochemistry, urinary protein electrophoresis and immunofixation, dosage of specific proteins, dosage of urinary enzymes or amino acids and genetics. More specialised tests may also be required, such as dosing renin-aldosterone activity, free water clearance for ADH deficiency and the determination of the amount of citrate in the urine in hypocitraturia [6,15]. The diagnostic certainty of CTIN is based on renal biopsy (RB) [5]. However, in most studies, histologic confirmation of CTIN cases is not always effective, and diagnosis is based on a series of presumptive arguments, as is the case in adults in Mali [10]. The aetiologies are diverse and varied in the literature [6,16]. Murray and al described anatomical defects in 30.7%, and analgesic abuse in 19.8% [11]. In our study, various tubulopathies such as Lowe syndrome, Bartter syndrome, nephrogenic diabetes insipidus and nephronophthisis were identified. The under-investigated nephrocalcinosis in our study could indicate renal tubular

acidosis, hyperoxaluria or another cause of hypercalciuria. We can therefore confirm that the tubulopathies described in the literature appear to exist in children in Senegal.

Table 1: *Distribution of 64 cases of CTIN by clinical signs at admission.*

Revealing clinical signs	N	%
Lumbar pain	18	28.1
HBP	11	17 .2
Fever	10	15.6
Ocular abnormalities	10	15 .6
Stunting	10	15.6
Polyuropolydipsia	8	12.5
Proteinuria	8	12.5
Dehydration	6	10
Urine retention	4	6.3
Leukocyturia	3	4.7
Burning urination	3	4.7
Haematuria	2	3.1
Dental abnormalities	2	3.1

Table 2: *Biological signs of CTIN in our patients.*

Revealing biological profiles		Number analysed	Average	Standarddeviation
Biological Blood Signs	Protidemia (g/l)	11	71.2	± 10,1
	Blood urea (g/l)	47	0.82	± 0,98
	Creatinine (mg/l)	55	31.5	± 51
	GFR (ml/min/1.73m^2)	49	48.3	± 33
	Hemoglobin level (g/dl)	48	10.5	± 3,2
	Natremia (mmol/l)	45	138.5	± 9,5
	Kaliemia (mmol/l)	45	4.6	± 1,0
	Chloremia (mmol/l)	45	104	± 1,0
	Blood glucose (g/l)	5	0.86	± 0,7
	Blood calcium (mg/l)	36	91.1	± 15,4
	Phosphoraemia (mg/l)	29	56.5	± 19,1
	Magnesium (mg/l)	29	59.4	± 14,4
	Uricemia (mg/l)	7	59.4	± 14,4
	Vitamin D (25-OH) (µg/L)	12	25.7	± 12,0
	PTHi (pmol/L)	12	422.9	± 624
Urine biological	Proteinuria (mg/kg/24 h)	15	58.6	± 60,1

signs	Leukocytes/min	5	51303	±45496
	Red blood cells/min	5	26704	± 29942

Table 3: *Distribution of CTIN cases by etiology.*

Etiology of CTINs among Children in Dakar		N (%)
Hereditary tubulopathies (50%)	Nephronophthisis	8(12.5)
	Cystinosis	2(3,1)
	Lowe syndrome	1(1.6)
	Mitochondrial cytopathy	1(1.6)
	Cystinuria	1(1.6)
	Bartter's syndrome	1(1.6)
	Claudine 16 mutation	1(1.6)
	Uric acid lithiasis	2(3,1)
	Diabetes insipidus	2(3,1)
	Unknown nephrocalcinosis	13(20, 3)
Polycystic kidney disease (3.1%)	Autosomal dominant polycystic disease	2(3,1)
Reflux nephropathies (18.8%)	Posterior urethral valve	5(7.8)
	Congenital megaureter	1(1.6)
	Vesicoureteral reflux	1(1.6)
	Hydronephrosis/Prune Belly syndrome	1(1.6)
	Undetermined uropathies	4(6.3)
Infectious CTINs (3.1%)	Chronic pyelonephritis (sequelae)	2(3,1)
Inflammatory CTINs (1 .6%)	Sickle cell disease	1(1.6)
Undetermined CTINs (23.4%)	Other undetermined CTINs	15(23.4)

The challenge is, on the one hand, screening with accessible means and, on the other hand, the availability of specific tests for each suspected case of tubulopathy and genetics. On evolution, proteinuria and anemia were factors associated with the presence of chronic kidney failure. Screening and early treatment of aenemia and proteinuria could improve the prognosis of renal function in our patients. Dialysis was performed in 12.5% of the children. In the study conducted in the USA by Deloumeaux and al., emergency dialysis was initiated in only 46.5% of patients with end-stage CKD [17]. Late initiation of dialysis was a factor associated with death in this study. It is therefore necessary to further develop dialysis techniques and make kidney transplant effective for children in Senegal.

Conclusion

CTINs accounted for less than one-tenth of the causes of chronic kidney disease in children in our study. Hereditary tubulopathies and reflux nephropathies were the primary etiologies of CTINs. Proteinuria and aenemia were the evolutionary factors leading to chronic kidney failure. Limited access to genetics and specific blood and urine tests were the major limitations in this study. Hence the need to make available the diagnostic tools of CTINs in children in Dakar.

Authors' contribution

Keita Y, Faye M and Dione S initiated the study and wrote the proposal and the first version of the manuscript. Cleaning the data collected for analysis was performed by Keita Y and Ndongo AA. All authors were involved in critically revising the manuscript and approved the manuscript before submission.

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Conflict of Interest

The authors have no conflict of interest to declare.

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