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Research Paper

Etiologies and Short-term Outcome of Medullary Nephrocalcinosis in Children

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ABSTRACT

Background and Aim: Hypercalciuria, hyperoxaluria, hereditary renal tubular disorders, and drug intoxication are the etiologies of nephrocalcinosis (NC) in children. This study aimed to determine the etiologies and short-term outcomes (resolution rate) of NC.

Methods: Children aged ≤18 years with NC who were referred to the nephrology clinic of an academic center from March 2003 to 2019 were considered for the study. The inclusion criteria were measurement of serum creatinine, sodium, potassium, calcium, and phosphorus; blood gas analysis; and random or 24-hour urine samples for creatinine and calcium levels.

Results: A total of 43 patients met the inclusion criteria. There were 21 girls (48.8%). The median age of patients was two years (10 months to 8 years). They were followed up for a median of 9 months (1-34 months). Most cases had medullary NC grade I (76.8%). The most common etiologies of NC were unknown (41.8%), idiopathic hypercalciuria (34.9%), and idiopathic hyperoxaluria (18.6%), respectively. Seven cases (16.3%) had mixed abnormalities. Resolution of NC at a follow-up of ≥ one year was uncommon (20%).

Conclusion: Idiopathic hypercalciuria and idiopathic hyperoxaluria were the most common identified etiologies. Hereditary tubular disorders accounted for 16.3% of the cases. Resolution of NC was uncommon, even in NC grade I, at a follow-up of ≥ one year.

Keywords: Medullary, Nephrocalcinosis (NC), Hypercalciuria, Hyperoxaluria, Distal renal tubular acidosis, Outcome

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Introduction

Nephrocalcinosis (NC) is the deposition of calcium oxalate and calcium phosphate in the renal parenchyma and kidney tubules. Localized calcium deposition due to focal kidney damage does not include NC. Most cases are asymptomatic. Symptomatic cases present with renal colic, polyuria, and polydipsia [1]. Types of NC include molecular, chemical, microscopic, or macroscopic. Based on the area involved, it is classified as medullary, cortical, and diffuse [1-3]. Increased excretion of calcium, phosphorus, or oxalate in the urine is a cause of NC. The most common cause is increased excretion of calcium in the urine with or without hypercalcemia [2-7]. Primary and secondary oxalosis and renal allograft rejection are the main etiologies of cortical NC [4-6]. Renal tubular acidosis type 1 (RTA1), primary hyperoxaluria, Bartter syndrome, primary hyperparathyroidism, high serum levels of vitamin D, medullary sponge kidney, low birth weight, hypophosphatemic rickets, chronic hypokalemia, loop diuretics, Dent disease, familial hypomagnesemia with hypercalciuria, and idiopathic hypercalcemia of infancy are the etiologies of medullary NC [8-17].

A recent study demonstrated a lower initial estimated glomerular filtration rate (eGFR) in patients with NC grade 3 compared to those with grade 1. In addition, the median eGFR decreased significantly at the last follow-up in cases without improvement in NC [18]. The current study was designed to demonstrate the etiologies and short-term outcomes (resolution rate) of medullary NC in children.

Materials and Methods

A retrospective cross-sectional study was conducted among children ≤18 years old with a diagnosis of medullary NC. The patients were referred to the nephrology clinic of a tertiary academic hospital from March 2003 to March 2019. The diagnosis of NC was made using kidney ultrasound (US). The kidney US apparatus was an Estate Class C (Italy) or a Samsung H60 (Korea) ultrasound with convex probes at 3.5 and 5 MHz. Medullary NC was graded as grade 1 (mild increase in echogenicity of medullary pyramids), grade 2 (mild diffuse increase in echogenicity of medullary pyramids without acoustic shadowing), and grade 3 (more homogeneous increase in echogenicity of medullary pyramids with acoustic shadowing) [19]. The primary outcome of the study was to define the etiologies with respect to the patients' age and the severity of medullary NC. The secondary outcome was to evaluate the changes in the severity of medullary NC at short-term follow-up (≥ six months). The inclusion criteria included a preliminary metabolic evaluation, including measurements of serum creatinine, sodium, potassium, calcium, and phosphorus; blood gas analysis; and random or 24-hour urine sampling for creatinine and calcium levels.

The criteria for diagnosing renal tubular disorders were as follows: Distal RTA: hyperchloremic metabolic acidosis and high urine pH (>6) [20]. Bartter syndrome: hypochloremic metabolic alkalosis, hypokalemia (potassium <3.5 mEq/l), normal blood pressure, and urinary chloride excretions >35 mEq/l [21]. Hypophosphatemic rickets: low serum phosphorus, normal calcium, normal or slightly elevated parathyroid hormone (PTH), and normal 1, 25 (OH) 2D3 [22]. Hypercalciuria and hyperoxaluria were defined based on the patients' ages (Table 1) [23]. Idiopathic hypercalciuria was defined as excessive urinary calcium excretion, normal serum calcium level, and the absence of secondary causes of hypercalciuria. Idiopathic hyperoxaluria was considered when no underlying causes of hyperoxaluria were identified. In the case of hypercalcemia (serum calcium ≥10.2 mg/dL), serum levels of vitamin D and PTH were measured. Checking serum creatinine levels was recommended yearly or at shorter intervals depending on the case.

Protocols of treatment

The treatment was designed to address the etiology of medullary NC. In patients diagnosed with idiopathic hypercalciuria, hydrochlorothiazide was recommended at a dose of 1-2 mg/kg/day. Vitamin B6 was prescribed in patients with hyperoxaluria at a dose of 5 mg/kg/day.

Statistical analysis

SPSS software, version 16 was used for data analysis. Tables and graphs were applied to present descriptive statistics. The normality of variables was tested using a one-sample Kolmogorov-Smirnov test. The Wilcoxon test was used to compare weight-for-age Z scores before starting treatment with those after receiving special treatment/treatments for NC. $P<0.05$ was considered significant.

Results

The medical files of 8398 patients referred to the nephrology department were evaluated. On initial evaluation, kidney US revealed medullary NC in 49 cases (0.6%). Laboratory examinations were available for 43 cases, and these cases were included in the study. They included 22 boys (51.17%) and 21 girls (48.83%). The median age of patients was two years, with an interquar-

Table 1. The definitions of hypercalciuria and hyperoxaluria utilized in the study [23]

Age (y)	Ratios of Random Urine Calcium to Random Urine Creatinine (mg/mg)	Age	Ratios of Random Urine Oxalate to Random Urine Creatinine (mg/mg)
0-1	≥0.81	<6 months	>0.29
1-2	≥0.56	6 months–2 y	>0.2
2-3	≥0.5	2–5 y	>0.11
3-5	≥0.4	6–12 y	>0.06
5-7	≥0.3	>12 y	>0.03
7-10	≥0.25		
10-17	≥0.24		

tile range (IQR) of 10 months to eight years. The median follow-up was 9 months (IQR, 1-34 months), ranging from 1 to 127 months. The frequencies of cases in age groups ≤6 months, 7-24 months, 3-5 years, and >5 years were 10(23.25%), 6(14%), 10(23.25%), and 17(39.5%), respectively. Table 2 presents the clinical manifestations in patients. Serum calcium concentration was within normal ranges in all patients. Before referral to the nephrology clinic, serum PTH and vitamin D levels were measured in 18(41.8%) and 24(55.8%) patients, respectively. Vitamin D deficiency (levels ≤10 ng/mL) in seven (16.3%), insufficient serum vitamin D levels (11-29 ng/mL) in 10(23.25%), and normal values in eight patients (18.6%) were noted. Serum PTH levels were within normal ranges (14 to 65 pg/mL) in 16 cases, and two patients with hypophosphatemia rickets+hypercalciuria had high serum PTH levels (113 and 70 pg/mL).

All patients <2 years were receiving vitamin D supplements, and phosphate supplements were administered in cases with hypophosphatemia rickets. Pediatric endocrinologists recommended calcium supplementation in seven cases, including five patients with hypercalciuria (two with hypophosphatemia rickets and three cases with idiopathic hypercalciuria). The median serum creatinine (Cr) concentration at presentation was 0.64 mg/dL (IQR, 0.5, 0.78 mg/dL). Serum creatinine concentrations ≥1 mg/dL (1.2-1.46 mg/dL) were found in five cases (11.6%) at presentation (two cases with idiopathic NC, one patient with idiopathic hypercalciuria, and one with idiopathic hyperoxaluria, and one with distal RTA). The serum creatinine levels at the last follow-up were ≥1 mg/dL (1.1-1.66 mg/dL) in four cases (9.3%). Three had grade III NC and nephrolithiasis. Serum creatinine concentration increased at follow-up in one patient with distal RTA. The patient's heights at the final visits were

Table 2. The clinical manifestations of NC in the enrolled patients

Clinical Manifestations	No. (%)
Asymptomatic cases[a]	11(25.6)
Gross hematuria	10(23.2)
Growth retardation	8(18.6)
Abdominal pain	6(14)
Urinary tract infection	3(6.9)
Dysuria	2(4.6)
Urine discoloration (crystalluria)	2(4.6)
Flank pain	1(2.3)
Increased urinary frequency	1(2.3)
Bone deformity	1(2.3)
Difficult voiding	1(2.3)
Polyuria and polydipsia	1(2.3)
Total cases	43(100)

[a]Kidney ultrasound was performed as a check-up. One case had a history of antenatal hydronephrosis.

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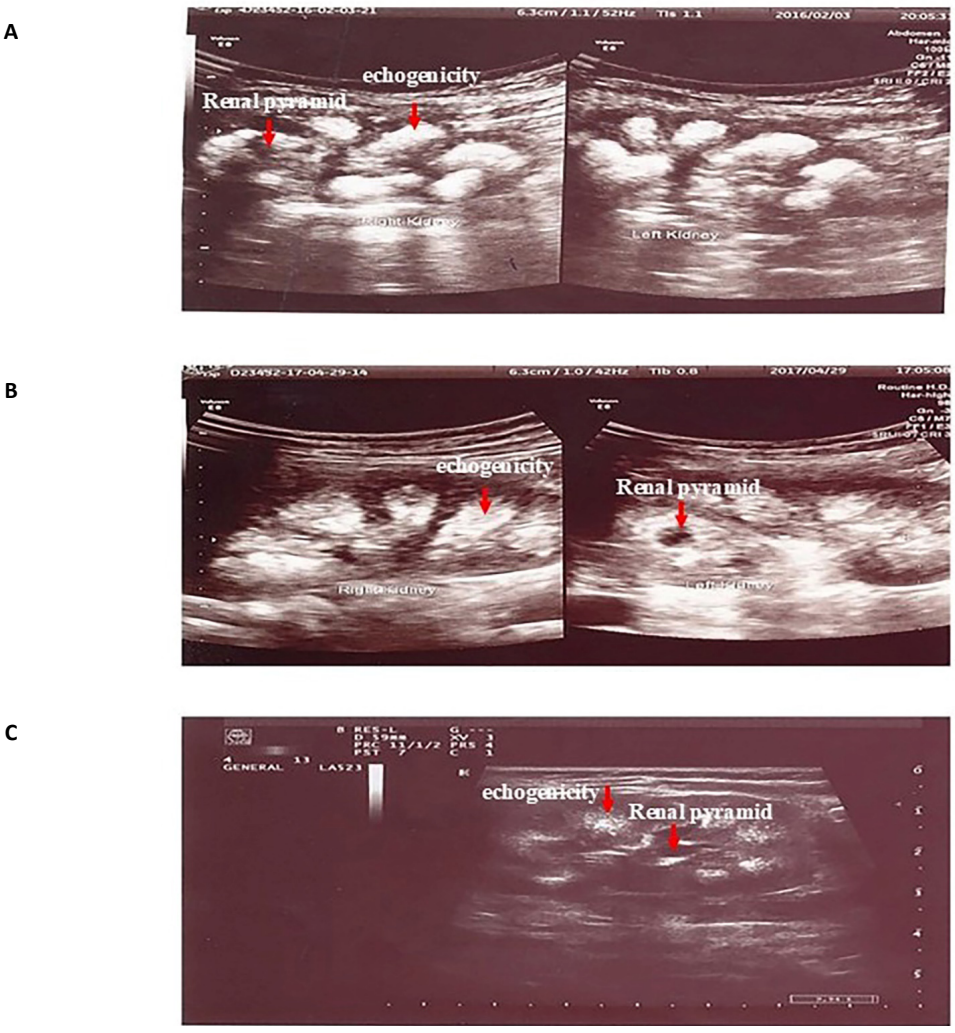

Figure 1. Nephrocalcinosis in kidney ultrasonography

A) A 4.5-month-old boy, with bilateral enlarged and echogenic kidneys at prenatal sonography: The kidney ultrasound revealed bilateral grade III NC. Urine oxalate/urine creatinine was 0.3 mg/mg (idiopathic hyperoxaluria).

B) A six-month boy referred with growth retardation (W=4 kg, and birth weight of 2.6 kg): At the initial evaluation, kidney US demonstrated Grade I medullary NC. The serum creatinine level was 0.31 mg/dL. Laboratory investigations showed hyponatremia, hypokalemia, and metabolic alkalosis (Bartter syndrome).

C) A 3.5 –year boy referred to the clinic with growth retardation (weight of 11.8 kg), polyuria, and polydipsia: The kidney US showed grade I medullary NC. The first evaluation revealed serum creatinine levels of 1.46 mg/dL, mild hypokalemia (serum potassium 3.4 meq/L), and normal blood gas analysis. Random urine Ca/Cr and oxalate /Cr ratios were within normal ranges for the age. The etiology of NC remained unknown.

not recorded in many cases; thus, we could not measure eGFR at the final follow-up.

A positive family history of nephrolithiasis was observed in 15 patients (34.9%). Nine (60%) had nephrolithiasis at presentation. NC grades I, II, and III were found in 33 cases (76.8%), 1 case (2.3%), and 9 cases (20.9%), respectively. Medullary NC was associated with nephrolithiasis in 16 patients (37.2%). Figures 1A, 1B and 1C present ultrasound images of three patients.

Growth at the initial and the last visit

At the initial evaluation, the median weight-for-age Z-score was -2.6 (-3.2, -1.7). It was <-1 in 21 patients (48.8%). The etiologies of NC in these patients were unknown (n=11, 52.4%), idiopathic hypercalciuria (n=6, 28.6%), idiopathic hypercalciuria and hyperoxaluria (n=2, 9.5%), Barter syndrome, and distal RTA (each n=1, 4.75%). The grade of NC was III in six patients (28.6%).

Table 3. Causes of NC in the enrolled patients

Etiology	No. (%)
Unknown	18(41.8)
Idiopathic hypercalciuria	9(20.9)
Idiopathic hyperoxaluria	3(7)
Mixed disorders	7(16.3)
Distal RTA[a] Hypophosphatemic rickets	3(7) 1(2.3)
Suspected of Dent disease Bartter syndrome	1(2.3) 1(2.3)
Total patients	43(100)[b]

[a]Renal tubular acidosis, [b]Four cases had idiopathic hypercalciuria and hyperoxaluria, and one with RTA had hyperoxaluria. Two patients with hypophosphatemic rickets had hypercalciuria.

At follow-up, the weights of the patients were recorded in 27 cases (62.8%); eight (29.6%) had a weight-for-age Z score <-1 (-2.8±1.22), including two with NC grade III. The etiologies of NC were unknown (n=4, 50%), idiopathic hypercalciuria (n=2, 25%), idiopathic hypercalciuria and hyperoxaluria (n=1, 12.5%), and Barter syndrome (n=1, 12.5%). The abnormal weight-for-age Z score <-1 was 48.8 % (21 out of 43) at presentation, which reached 29.6% (8 out of 27) at the last follow-up. The median (IQR) weight-for-age Z score was -0.8 (-2.1, 0.1), which reached -0.36(-1.9, 0.8) (P=0.011; Wilcoxon test). The weight-for-age Z scores significantly increased during follow-up.

Etiologies of medullary NC

The etiology of NC was not determined in 18 patients (41.8%). None of the participants underwent genetic testing to determine the etiology of NC (e.g. primary hyperoxaluria). The genetic tests were either unavailable (especially in the first years of the study) or were expensive.

The etiologies of NC, across different age groups, and by degree of NC were assessed (Tables 3, 4 and 5). In total, the most commonly identified etiologies for NC were idiopathic hypercalciuria (n=15, 34.9%), idiopathic hyperoxaluria (n=8, 18.6%), and distal RTA (n=4, 9.3%) (Table 3). The most commonly identified etiology of NC across all age groups was idiopathic hypercalciuria, except in the 7-24 months age group (Table 4). Idiopathic hypercalciuria was the most frequently identified etiology for all grades of NC (Table 5). Idiopathic hypercalciuria (n=15) was associated with idiopathic hyperoxaluria in four patients (26.6%). Idiopathic hyperoxaluria (n=8) was accompanied by idiopathic hypercalciuria in four (50%). Urine oxalate in random or 24-hour urine was not measured in 15 patients (34.9%), including 8 cases with idiopathic hypercalciuria (44.5%). Most cases of idiopathic hypercalciuria and idiopathic hyperoxaluria were diagnosed at age >5 years (Table 4).

Patients with nephrolithiasis (n=16)

An underlying disorder was identified in 12(75%), including idiopathic hypercalciuria, idiopathic hyperoxaluria, distal RTA, and hypophosphatemic rickets in five (31.25%), four (25%), two (12.5%), and one case (6.25%), respectively. The NC was grade III in four (25%). Urine oxalate assessment was performed in only 10 patients (62.5%).

Degree of NC

Five of nine cases (50%) had NC grade III at diagnosis and were aged >5 years. Table 5 presents the etiologies of NC regarding its degree. The most common underlying disease in patients with NC grade III was idiopathic hypercalciuria (44.5%), whereas in NC grades I-II, the underlying disease was unidentified (Table 5). Random or 24-hour urine oxalate was assessed in four cases (44.4%) with grade III NC and was high in one. Grade III NC was accompanied by nephrolithiasis in four patients (44.4%). In asymptomatic cases (n=11), the underlying diseases diagnosed after laboratory examinations were idiopathic hypercalciuria (n=7, 63.6%), idiopathic hyperoxaluria (n=2, 18.2%), and hypophosphatemic rickets (n=2, 18.2%). All patients had weight-for-age Z scores within normal ranges. Medullary NC was accompanied by nephrolithiasis in seven cases (63.6%). Four cases (36.4%)

Table 4. Causes of NC related to different age groups

Age Group	Etiology of NC	No. (%)
≤6 months	Unknown	5(40)
	Idiopathic hypercalciuria	3(30)
	Distal RTA[a]	1(10)
	Bartter syndrome	1(10)
	Total patients	10(100)
7-24 months	Unknown	5(83.6)
	Idiopathic hyperoxaluria	1(16.7)
	Total patients	6(100)
3-5 years	Unknown	3(10)
	Idiopathic hypercalciuria	2(10)
	Distal RTA	2(20)
	Hypophosphatemic rickets	1(10)
	Hypophosphatemic rickets+ idiopathic hypercalciuria	1(10)
	Hyperoxaluria	1(10)
	Total patients	10(100)
>5 years	Idiopathic hypercalciuria	4(29.4)
	Unknown	5(23.5)
	Idiopathic hypercalciuria + hyperoxaluria	4(23.5)
	Idiopathic hyperoxaluria	2(11.8)
	Hypophosphatemic rickets+ idiopathic hypercalciuria	1(5.9)
	Distal RTA+ hyperoxaluria	1(5.9)
	Total patients	17(100)

[a]Renal tubular acidosis.

had NC grade III. Kidney US was recommended every three months for those with nephrolithiasis and every six months for other situations. Patients were followed up for a median of 9 months (IQR, 1-34 months). The median follow-up in cases with NC grade III was 26 months (IQR, 1-127 months). Table 6 presents the changes in NC grade at follow-up of ≥6 months and ≥1 year.

No change, decrease in grading, and resolution of NC were reported in 12(66.6%), three (16.7%), and three cases (16.7%) with NC grades I-II. Six (85.7%) and one (14.3%) cases with NC grade III showed no change and a decrease in NC grading, respectively (P=0.487). The etiologies of NC were evaluated in patients with no change in NC at follow-up ≥6 months (n=18). It included unknown (n=3, 16.6%), idiopathic hypercalciuria (n=6, 33.4%), idiopathic hypercalciuria and hyperoxaluria (n=7, 38.9%), distal RT, and Barter syndrome (n=1, 5.55%).

Discussion

We found idiopathic hypercalciuria (34.9%), idiopathic hyperoxaluria (18.6%), distal RTA (9.3%), and hypophosphatemia rickets (7%) to be the most common identified etiologies of NC. The etiology of NC was not identified in 41.8% of cases. In a follow-up of ≥ 6 months, we noted a resolution rate of 12%, including patients with NC grade I.

Joung et al. [9] evaluated 464 patients < 18 years with a diagnosis of NC; 75% were preterm infants. In a one-year follow-up, NC was resolved in 62%. Among patients with persistent follow-ups, 10.5% died without improvement

Table 5. Causes of NC regarding its severity

Etiology	No. (%)	
	NC Grade I-II	NC Grade III
Unknown	16(47)	2(22.2)
Idiopathic hypercalciuria	5(14.7)	4(44.5)
Idiopathic hyperoxaluria	2(5.9)	1(11.1)
Mixed abnormalities[a]	7(20.6)	0
Distal RTA[b]	1(2.95)	2(22.2)
Hypophosphatemic rickets	1(2.95)	0
Suspected of Dent disease	1(2.95)	0
Bartter syndrome	1(2.95)	0

[a]Four cases had idiopathic hypercalciuria and idiopathic hyperoxaluria, and one with RTA had hyperoxaluria. Two patients with hypophosphatemia rickets had hypercalciuria, [b]Renal tubular acidosis.

Table 6. Changes in the severity of NC observed at follow-up

Changes in NC	No. (%)	
	Follow-up ≥6 Months[a]	Follow-up ≥ One Year[b]
No change	17(65.4)	13(65)
Decreased grading of NC[c]	4(15.4)	3(15)
Resolution of NC	5(19.2)	4(20)
Total cases	26(100)	20(100)

[a]Median 23.5, IQR of 11.25 -69 months, [b]Median 40, IQR of 18.25 -80.25 months, [c]NC,

of NC, and 8.4% progressed to chronic kidney disease (CKD). The outcome of NC in preterm patients was generally favorable, with a high spontaneous resolution rate. Full-term children were at a significant risk of persistent NC and developing CKD. The authors did not evaluate patients for metabolic abnormalities and focused on underlying diseases. Our methodology differed from that of the above study. We evaluated patients to define hereditary tubulopathy or metabolic abnormalities (hypercalciuria and hyperoxaluria). They did not report the grade of NC. None of our cases had a history of prematurity. The drugs used recently were calcium or phosphorus supplements.

Ramya et al. [11] reported distal RTA (33.3%) as the most frequent etiology of NC. The most common presentation was with growth failure (53.7%). In our series, we did not find an etiology in 41.8%, and idiopathic hypercalciuria (34.9%) was the most commonly identified etiology. Growth failure was found in 48.8% at presentation.

Recent studies have shown that changes in kidney function do not differ by etiology [18, 24]. Rönnefarth et al. [19] found growth retardation (46%) as the main presentation, and idiopathic hypercalciuria (34%) as the most common etiology. In our series, growth retardation was as common as in the mentioned study (48.8%). The underlying diseases were unknown in 41.8% of the patients. However, similar to this study, idiopathic hypercalciuria was a common etiology (34.9%). Rönnefarth et al. [19] reported an increase in the NC grade during the follow-up. In our series, the NC grade did not increase during the follow-up. It means that NC grade I did not change to grade II or III, and NC grade II did not change to grade III.

Hoppe et al. [17] found a metabolic etiology for NC in up to 75% of patients. The most common etiology was hypercalciuria. In addition, most cases were asymptomatic. In our series, a metabolic disorder was found in 58.2% of the cases, and 25% of the patients were asymptomatic. In contrast to the mentioned study, the etiology

of NC remained unknown in most cases. In a study by Mantan et al. [25], growth retardation was observed in 82.5% of cases. Grade II-III NC was found in 70% of the cases, and 7.5% of patients had nephrolithiasis. The most common etiology for NC was distal RTA (50%). At a median follow-up of 35 months, no resolution of NC was reported. Three patients (7.5%) had CKD stage V during a follow-up of 18-84 months. We could not find an etiology for NC in 41.8%. Distal RTA was not a common etiology (9.3%). Most patients had NC grade I (76.7%). Grade II-III NC was found in 23.3% of the cases. Growth retardation was more frequent in their cases compared to our patients (82.5% versus 48.8%, respectively). None of our cases progressed to CKD stage V at the final follow-up.

We found a resolution of NC at a follow-up of ≥ one year in 20% of the patients. Differences in etiology, NC grading, and median follow-up may account for the different outcomes in our study compared to those reported by Manthan et al. [25].

In a study by Jellouli et al. [26], the most common symptom was growth delay. The mean follow-up was 3.5 years. Primary hyperoxaluria type I and distal RTA accounted for 65% and 20% of cases, respectively. At diagnosi ourse of renal failure was observed in 45% of patients. In our series, growth retardation was found in 48.8% at diagnosis; however, it was the reason for referral to the clinic in 18.6% of the patients. Gene analysis was not available; hence, none of the 8 patients (18.6%) with hyperoxaluria were evaluated for primary hyperoxaluria. However, the clinical course in those with idiopathic hyperoxaluria did not match primary hyperoxaluria. Their serum creatinine levels at presentation and final visits were 0.68±0.32 mg/dL and 0.8±0.38 mg/dL, respectively. Distal RTA was not a common etiology in our study (9.3%). Longer duration of follow-up, the difference in the etiology of NC, and the high frequency of primary hyperoxaluria in a study by Jellouli et al. [26] account for different outcomes compared to ours.

Similar to our study, Ammenti et al. [27] found NC accidentally in 24% of patients undergoing kidney ultrasound. The most common presentation was growth failure (41%). At a median follow-up of 4 years and 5 months, the growth standard deviation score improved from -2.2 to -1. The NC degree increased in 62% of cases. The most frequent etiology of NC was hereditary tubulopathies (41.5%). The etiologies of NC in our series were completely different. Hereditary tubulopathies were found in nine cases (20.9%). The degree of NC did not increase in any cases. The median weight-for-age Z score improved at follow-up (-0.8 at diagnosis, reaching -0.36 [P=0.011]).

Primary hyperoxaluria type 1 is symptomatic before the age of 10 years in >50% of cases. Although NC correlates with the development of renal insufficiency, it can occur even in patients with no NC [28]. Mortazavi et al. [29] found distal RTA (30.6%) as the most common etiology of NC. At a follow-up of 4.4±2.9 years, 20.9% had decreased GFR, and 6.5% with a diagnosis of hyperoxaluria developed end-stage renal disease. In our series, distal RTA was an uncommon etiology. The most commonly known etiology was idiopathic hypercalciuria (34.9%). We could not find an underlying disease in 41.8% of the patients. Different etiologies and a longer duration of follow-up (mean 4.4 years) in the study by Mortazavi et al. [29] may account for the different outcomes compared to our series. Distal RTA has been reported as the etiology of NC in 20% [26], 30.6% [29], 32% [28], and 50% [25] of cases. In our series, it accounted for 9.3% of NC.

The main limitations of our study were the retrospective design, the lack of oxalate measurements in many patients, the absence of genetic confirmation of suspected hereditary disorders, and the relatively short follow-up period. In addition, we could not measure the eGFR at the final visits because the patients' heights were not recorded. However, determining the etiology of NC based on age group and severity of NC is the main advantage of the current study.

Conclusion

In our study, the cause of NC remains unknown in 41.8% of cases. The most commonly identified etiology was idiopathic hypercalciuria. Growth retardation was frequently observed. Additionally, more than one-third of the patients had an association between NC and kidney stones. In patients with a follow-up ≥1 year (median follow-up 40 months), NC resolved in only 20% of cases.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1397.142).

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Authors' contributions

Conceptualization and supervision: Mitra Naseri andAsal Mir; Methodology: Mitra Naseri; Data collection: Asal Mir, Mitra Naseri, and Nooshin Tafazoli; Data analysis; Investigation and writing: All authors; Funding acquisition and resources: Mitra Naseri.

Conflict of interest

The authors declared no conflict of interest.

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