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A nationwide retrospective study in Turkish children with nephrocalcinosis

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Background/aim: Nephrocalcinosis (NC) is defined as calcium deposition in the kidney parenchyma and tubules. This study aims to determine the etiology, risk factors, and follow-up results of patients with NC in Turkey.

Materials and methods: Patients diagnosed with NC in the pediatric nephrology Department Units of 19 centers from all geographical regions of Turkey over a 10-year period (2010–2019) were included in the study. The medical records from the centers were reviewed and demographic data, admission complaints, medical history, systemic and genetic disorders, risk factors for NC, treatment details, and presence of NC after one-year follow-up, were recorded retrospectively.

Results: The study sample included 195 patients (88 females, 107 males). The mean age at diagnosis was 39.44 ± 47.25 (0.5–208) months; 82/190 patients (43.2%) were diagnosed incidentally; 46/195 patients (23.6%) had an underlying disease; idiopathic hypercalciuria was detected in 75/195 (38.4%) patients. The most common systemic diseases were distal renal tubular acidosis in 11/46 patients (23.9%), primary hyperoxaluria in 9/46 patients (19.6%) and Bartter syndrome in 7/46 patients (15.3%). After one year of follow-up, NC resolved in 56/159 patients (35.2%) and they all did not have an underlying systemic disease.

Conclusion: The most common presentation of NC was incidental. Distal renal tubular acidosis and primary hyperoxaluria were the main systemic diseases leading to NC, while hypercalciuria was the most common metabolic risk factor. Nephrocalcinosis was found to remain in most of the patients at a one-year follow-up. It may resolve particularly in patients with no underlying systemic disease.

Keywords: Bartter syndrome, hypercalciuria, nephrocalcinosis, renal tubular acidosis

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1. Introduction

Nephrocalcinosis (NC) is defined as calcium accumulation in the kidney parenchyma and tubules [1]; it is classified as molecular (chemical), microscopic or macroscopic and can be seen in radiological imaging [1,2]. Molecular NC is generally observed in patients with hypercalcemia and resolves after the correction of hypercalcemia. Microscopic NC may present in patients who use phosphate preparations for bowel cleansing [3]. Nephrocalcinosis can also be classified as medullary and cortical according to the anatomical localization of the calcium deposition. Cortical NC accounts for approximately 3% of NC cases, such as renal cortical necrosis or chronic glomerulonephritis [1–5]. Medullary NC accompanies patients with distal renal tubular acidosis, primary hyperoxaluria, primary hyperparathyroidism, medullary sponge kidney, and inherited tubulopathies.

The renal prognosis of NC depends on the underlying cause. While most patients with NC do better, diseases such as primary hyperoxaluria type 1 could lead to end-stage renal disease [6], so determining the underlying disease is important for predicting the outcome and treatment decision. The present study determines the etiologies, risk factors, follow-up, and treatment of patients with NC in a large number of centers in Turkey.

2. Materials and methods

Nephrocalcinosis patients of 19 Pediatric Nephrology Department Units (Mersin University Medical Faculty, Bakırkoy Dr Sadi Konuk Education and Research Hospital, Kayseri City Hospital, İstanbul University Medical Faculty, Cerrahpaşa Medical Faculty, Marmara University Education and Research Hospital, Kartal Dr. Lütfi Kırdar City Hospital, Mediterranean University Medical Faculty, Gazi University Medical Faculty, Ondokuz Mayıs University Medical Faculty, Bursa Dörtçelik Children Hospital, İstanbul Haseki Education and Research Hospital, Erzurum Education and Research Hospital, Erciyes University Medical Faculty, Manisa Celal Bayar University Medical Faculty, Anadolu Medical Center, Bahçeşehir University School of Medicine, Konya, Dr Faruk Sukan Obstetrics and Children Hospital, Eskişehir City Hospital) over a 10-year period (2010–2019) were included in the study. Mersin University Ethics Committee approved the study (2018/245). The medical records of each center were reviewed and demographic data, admission complaints, medical history, systemic and genetic disorders, risk factors for NC, treatment details, and whether NC was still present after a one-year follow-up were recorded retrospectively. Patients who received loop diuretics were excluded from the study. Nephrocalcinosis diagnosis was based on the identification of increased echogenicity on ultrasound; hypervitaminosis D was defined if 25(OH)D levels were above 100 ng/mL [7,8]; primary hyperoxaluria was defined as urinary oxalate increment with confirmed genetic analysis; secondary hyperoxaluria was defined as hyperoxaluria secondary to chronic ingestion of excessive amounts of oxalate precursors; distal renal tubular acidosis (dRTA) was defined as hypokalemic hyperchloremic metabolic acidosis, hypercalciuria, and urine pH > 5.5; Bartter syndrome was defined as hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypercalciuria with NC; familial hypomagnesemia-hypercalciuria was defined as persistent hypomagnesemia, incomplete distal tubular acidosis, hypercalciuria, and NC; medullary cystic disease was diagnosed in patients with urine concentrating defects, a positive family history for renal cysts, and the presence of medullary cysts and/or increment medullary echogenicity in ultrasonography; primary hyperparathyroidism was defined as chronic increment of calcium levels and parathyroid hormone (PTH) [9]; hypophosphatemic rickets was diagnosed in patients with phosphaturia, hypophosphatemia, rickets with inactivating mutations in the phosphate regulating gene (PHEX with homologies to endopeptidases on the X chromosome); idiopathic hypercalciuria was defined as elevated urinary calcium excretion without concomitant hypercalcemia and systemic disease; hypercalciuria was defined for calcium/creatinine ratio levels in urine samples according to age groups (0–6 months: >0.8 mg/mg, 7–12 months: >0.6 mg/mg, 1–3 years: > 0.53 mg/mg, 3–5 years: > 0.39 mg/mg, 5–7 years: >0.28 mg/mg and >7 years: >0.21, hyperoxaluria was defined for oxalate/creatinine levels in spot urine samples according to age groups (0–6 months: >0.28 mg/mg, 7–24 months: >0.11 mg/mg, 2–5 years: >0.08 mg/mg, 5–14 years: >0.06 mg/mg, >16 years: >0.03 mg/mg); hypocitraturia was defined as a citrate/creatinine ratio in spot urine samples according to age groups (≤5 years: <0.42 mg/mg, >5 years: <0.25 mg/mg hyperuricosuria was defined as uric acid/creatinine levels in spot urine samples according to age groups (< 1 year: >2.2 mg/mg, 1–3 years: >1.9 mg/mg, 3–5 years: >1.5 mg/mg, 5–10 years: >0.9 mg/mg and >10 years: >0.6 mg/mg; and cystinuria was defined as cystine/creatinine levels in spot urine samples according to age groups (< 1 month: >0.18 mg/mg, 1–6 months: >0.11 mg/mg and > 6 months: >0.038 mg/mg [10]. Renal failure referred to stage 3–5 chronic kidney disease.

2.1. Statistical analysis

The data analysis was conducted using SPSS v: 21.0 software. Descriptive statistics were presented as mean ± standard deviation. An independent-sample t test was used to compare the means between age of the groups. The dependency between categorical variables was tested using Pearson's chi-square test and Fisher exact chi-square test. Numbers and percentages were used to express descriptive statistics. A p value < 0.05 was considered statistically significant.

3. Results

The study was conducted with 195 patients from 19 different centers in Turkey (88 females, 107 males). The mean age at diagnosis was 39.44 ± 47.25 (0.5–208) months. Fourteen patients (7.2%) were diagnosed in neonatal period.

3.1. Presentation and clinical characteristics of patients with NC

Incidental diagnosis was made on 43.2% patients (82/190), while 56.8% (108/190) had admission complaints such as vomiting (n = 30, 15.8%), restlessness (n = 24, 12.6%), abdominal pain (n = 21, 11.0%), failure to thrive (n = 12, 6.3%), fever (n = 10, 5.3%), hematuria (n = 7, 3.7%), and dysuria (n = 4, 2.1%). Prematurity and hospitalization history were present in 16.2% (31/191) and 28.0% (53/189) of the patients, respectively. Consanguinity was present in 70/186 (37.6%) cases. A family history of stones was present in 90/186 (48.4%) patients.

Vitamin D therapy was received by 43.5% (80/184) of the patients, 69 (86.2%) were taking 400–600 IU/day and 11 (13.8%) were taking greater than 600 IU/day. The mean of the $25(OH)_2D_3$ levels of the patients was 29.99 ± 37.29 (7.00–334.40) ng/mL. Vitamin D levels were lower than 30 ng/mL, 30–100 ng/mL, >100 ng/mL in 86/135 (63.7%), 47/135 patients (34.8%), and 2/135 (1.5%) patients, respectively.

Growth retardation was present in 42/185 (22.7%), renal failure in 7/185 (3.8%) and hypertension in 7/185 (3.8%) patients. Growth retardation was present in 13/30 patients with systemic diseases (43.3%); 6 had Bartter syndrome, 5 had dRTA, and 2 had Williams syndrome. In preterm patients, growth retardation was observed in 12/31 (38.7%) patients. All of the patients with renal failure (n = 7) had systemic diseases; three had Bartter syndrome, three had primary hyperoxaluria and one had dRTA. Liddle syndrome was detected in one patient who had hypertension, while 6 patients had no detectable systemic disease leading to hypertension.

Nephrolithiasis/urolithiasis (NL/UL) was accompanying 101/195 (51.8%) patients with NC. Eighteen (17.8%) of those patients had systemic disease, while 83 (82.2%) had no systemic disease.

3.2. Etiologic factors and metabolic risk factors leading to nephrocalcinosis

Etiologic factors of patients with NC were shown in Table 1. Systemic diseases (dRTA, primary hyperoxaluria, Bartter syndrome, familial hypomagnesemia and hypercalciuria, medullary sponge kidney, primary hyperparathyroidism, hypervitaminosis D, Williams syndrome, hypophosphatemic rickets, Liddle syndrome, enamel renal syndrome, down syndrome, glucose-galactose malabsorption, and tumor lysis syndrome) were present in 46/195 (23.6%) patients. Idiopathic hypercalciuria was detected in 75 (38.46%) patients, while there was no detectable underlying reason in remaining 74 (37.95%) patients (Table 1).

Table 1. Etiologic factors of patients with NC.

Diseases	n= 195	%
Idiopathic hypercalciuria	75	38.46
Distal renal tubular acidosis	11	5.64
Primary hyperoxaluria	9	4.61
Bartter syndrome	7	3.59
Familial hypomagnesemia and hypercalciuria	3	1.54
Medullary sponge kidney	3	1.54
Primary hyperparathyroidism	2	1.03
Hypervitaminosis D	2	1.03
Williams syndrome	2	1.03
Hypophosphatemic rickets	2	1.03
Liddle syndrome	1	0.51
Enamel renal syndrome	1	0.51
Down syndrome	1	0.51
Glucose-galactose malabsorption	1	0.51
Tumor lysis syndrome	1	0.51
Unknown etiology	74	37.95

Hypercalciuria was the most common metabolic risk factor accompanying NC, being detected in 95/195 (48.7%) patients, while the other metabolic risk factors were hypocitraturia and hyperoxaluria in 48/163 (29.4%) and 29/164 (17.7%) patients, respectively (Table 2). Hypercalciuria ratio in patients who received vitamin D therapy without systemic disease was 40/83 (48.2%). Hypercalciuria with hypercalcemia was detected in 20/164 (12.2%) patients. Three of the patients with hypocitraturia had dRTA, and three had Bartter syndrome. Remaining 42 had idiopathic hypocitraturia. Nine of the patients with hyperoxaluria had primary hyperoxaluria, while the remaining 20 patients were found to have secondary hyperoxaluria.

3.3. Medications of the patients with NC

The medications were potassium citrate in 136/193 (70.4%) and thiazide diuretics in 28/183 (15.3%) patients. Furthermore, two patients (22.2%) with primary hyperoxaluria type 1 (n = 9) were on vitamin B6 treatment and underwent a liver transplantation. No patient with primary hyperparathyroidism underwent parathyroidectomy. Other treatments noted were oral potassium, sodium, indomethacin for Bartter syndrome, and alkaline supplements for RTA.

3.4. One-year follow-up results of patients with NC

At one-year follow-up (n = 159), no NC was found in 56 (35.2%) patients and none had any systemic disease. Nephrocalcinosis was still present in 103/159 (64.8%)

Table 2. Metabolic risk factors for patients with NC.

Risk Factors	n	Patients*	%
Hypercalciuria	95	195	48.7
Hypocitraturia	48	163	29.4
Hyperoxaluria	29	164	17.7

*Number of patients who had data.

patients, of whom 46 (44.7%) had a systemic disease and 57 (55.3%) had no detectable underlying disease. Nephrocalcinosis resolved in six of eight patients (75%) who were diagnosed in neonatal period after one-year follow-up. Mean ages of the patients whose NC resolved and unresolved were 38.51 ± 53.41 and 42.26 ± 42.27, respectively. No statistically significant difference was observed between the ages of patients whose NC resolved and unresolved ($p = 0.628$). Statistically significant difference was observed in terms of systemic disease presence between patients whose NC resolved and unresolved ($p < 0.001$) (Table 3). No statistically difference was detected between patients who received potassium citrate treatment and who did not in terms of NC presence after one-year follow-up ($p = 0.091$) (Table 3). Also, there was no statistically difference in terms of sex, prematurity, consanguinity, vitamin D treatment, presence of hypercalciuria, hypocitraturia, and hyperoxaluria between patients whose NC resolved and unresolved ($p = 0.308$, 0.850, 0.433, 0.127, 0.584, 0.083, and 0.358, respectively) (Tables 3 and 4).

4. Discussion

The prevalence and incidence rates of NC in children are increasing [11]. In the United States, the incidence of NC is in the range of 36–57 per 100,000 populations [12], while there are no epidemiologic data on NC in children in Turkey. This study provides demographic data and details the etiology, risk factors and one year follow-up results of NC cases from 19 centers from all of the geographic regions, which are the largest NC series and a good sample of Turkey.

The patients in the present study were mostly diagnosed with NC incidentally, which is similar in literature [13]. Nephrocalcinosis is seen in 7%–41% of low birth-weight neonates, which has been attributed to such additional risk factors as the extended administration of loop diuretics, tubular dysfunction, prolonged oxygen need, hypoxemia, acidemia, hypovolemia, and nephrotoxic drugs [14]. The ratio of prematurity in patients with NC was not high (16.2%) in the study.

Vitamin D therapy is associated with NC and is known to lead to hypercalcemia and hypercalciuria [7]. Hypercalciuria ratio in patients who received vitamin D therapy without systemic disease was 48.2% in the present study. It can be considered that vitamin D treatment may have contributed to development of NC in approximately half of the patients.

In a study, the etiology of NC in Tunisian children was found to be primary hyperoxaluria type 1 (65%) and dRTA (20%) [15]. In the largest series of 375 patients with NC (1), the most frequent clinical diagnoses were hyperparathyroidism, dRTA and medullary sponge kidney, while approximately 7% of patients had no underlying disease. In the present study, 23.6% of the patients had a systemic disease, with dRTA, primary hyperoxaluria type 1 and Bartter syndrome being the most common. Idiopathic hypercalciuria, which has been identified as a common cause of NC in children, being seen in 13%–34% of patients with NC [7,16], was detected in 38.46% patients in the present study. Nephrocalcinosis in tumor lysis syndrome can be caused by hyperphosphaturia. Hypercalcemia and hypercalciuria leading to NC were detected in the patient with Down Syndrome. No underlying disease or metabolic risk factors causing NC could be identified in 37.95% patients, although they may have a genetic abnormality leading to NC. Longer follow-up results would give more information about underlying reasons.

Growth retardation was the most frequent clinical manifestation [15], being present in 43.3% of patients with systemic disease and 38.7% of patients who were preterm. Chronic metabolic acidosis in dRTA and hypercalciuria in Bartter syndrome leads to excessive bone demineralization causing growth retardation.

It is known that NL can occur in patients with NC who have systemic diseases such as dRTA, Bartter syndrome, and primary hyperoxaluria. In the present study, 18/46 (39.1%) of patients with systemic disease was accompanying with NL/UL. The literature has reported that NC can occur in patients who develop calcium oxalate stones but with no systemic disease [17]. Nephrolithiasis was found to accompany with NC in 83/101 (82.2%) patients without systemic disease, which is consistent with previous studies. This can be attributed to presence of hypercalciuria, which is an important underlying pathological process for both NC and NL [18].

The treatment of NC is directed by the underlying reason. For example, parathyroidectomy in the presence of primary hyperparathyroidism; increased fluid intake, restriction of sodium intake and thiazide diuretics if hypercalciuria is present; and potassium citrate treatment in those with hypocitraturia and a urine pH <7 [6]. Potassium citrate increases the solubility of calcium in urine and can limit NC. In the present study most of the patients were on potassium citrate treatment (70.4%). After one-year follow-up, there was no significant difference between patients who received potassium citrate and who

Table 3. Comparison of demographic, clinical characteristics, and potassium citrate treatments of the patients whose NC resolved and unresolved after one-ear follow-up (n = 159).

Variables		Nephrocalcinosis				p
		No		Yes		
		n	%	n	%	
Sex	Male Female	33 23	58.9 41.1	52 51	50.5 49.5	0.308
Prematurity	No	47	83.9	89	86.4	0.850
	Yes	9	16.1	14	13.6	
Consanguinity	No	38	67.9	62	60.2	0.433
	Yes	18	32.1	41	39.8	
Vitamin D treatment	No Yes	27 29	48.2 51.8	64 39	62.1 37.9	0.127
Systemic disease	No Yes	56 0	100.0 0.0	57 46	55.3 44.7	<0.001
Potassium citrate treatment	No	19	33.9	21	20.4	0.091
	Yes	37	66.1	82	79.6	

Table 4. Comparison of metabolic risk actors of the patients whose nc resolved and unresolved.

Variables		Nephrocalcinosis				p
		No		Yes		
		n*	%	n*	%	
Hypercalciuria	No Yes	26 30	46.4 53.6	52 50	51.0 49.0	0.584
Hypocitraturia	No Yes	37 10	78.7 21.3	55 33	62.5 37.5	0.083
Hyperoxaluria	No Yes	39 6	86.7 13.3	69 19	78.4 21.6	0.358

*Number of patients who had data.

did not in terms of NC presence. So, we can conclude that potassium citrate treatment is not effective on resolution of NC.

Nephrocalcinosis is a consequence of hypercalciuria. Increased urinary calcium load arises either through increased calcium absorption (extra-renal causes) or impaired calcium reabsorption within the renal tubule. Macroscopic NC rarely resolves. After treatment for hypercalciuria and following corrective intestinal surgery in hyperoxaluria, a partial reversal of NC has been reported [6]. On the other hand, it was demonstrated that neonatal-acquired NC resolves by 50% during the first year of life and to 75% by school age without having an impact on kidney function [19,20]. In the present study, after one-year follow-up, neonatal-acquired NC resolved in 75% of the patients, which is consistent with the literature. Nephrocalcinosis did not resolve in 103/159(64.8%) patients, of whom 46 (44.7%) had an underlying systemic disease. An unknown genetic abnormality can present 57/103 (55.3%) patients with no systemic disease and in whom NC was still present. Nephrocalcinosis resolved in 56/159 patients (35.2%) with no systemic diseases after a

follow-up of one year, which led us to conclude that NC may resolve particularly in patients with no underlying systemic disease.

The limitation of the present study is its retrospective design, which prevents the garnering of detailed data from all patients. Genetic analysis for detecting CYP24A1 mutations or SLC34A1 variants was not available in most of the centers. These mutations could have led to NC in some of the patients with no underlying disease. Prospective studies with a longer period follow-up may give more information about the etiology and prognosis of NC in Turkish children.

In conclusion, the most common presentation of NC was incidental. Distal renal tubular acidosis, primary hyperoxaluria, and Bartter syndrome were the main systemic diseases leading to NC. Hypercalciuria was the most common metabolic risk factor. Most of the patients were found to still have NC at a one-year follow-up. Nephrocalcinosis may resolve particularly in patients who did not have an underlying systemic disease.

Informed consent

This study was approved by Mersin University Ethics Committee (2018/245).

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