Renal function and linear growth of children with nephrocalcinosis: a retrospective single-center study

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SUMMARY: Doğan ÇS, Uslu–Gökçeoğlu A, Çomak E, Alimoğlu E, Koyun M, Akman S. Renal function and linear growth of children with nephrocalcinosis: a retrospective single-center study. Turk J Pediatr 2013; 55: 58-62.

The aim of this study was to analyze the etiology of nephrocalcinosis (NC) and whether it has any effect on growth and renal function in children. Forty-three children who were diagnosed with bilateral NC were studied retrospectively. Two neonates treated with furosemide and five premature infants were excluded from the study. The most common condition leading to NC was hereditary tubulopathies (50%). Data of 27 children who had a follow-up period of at least two years were examined in more detail. Of the 27 patients, the median age at first examination was 12 (range: 2-132) months and median follow-up time was 57 (range: 24-209) months. Thirteen of 27 (48.1%) patients had height standard deviation scores (hSDS) <-2 at presentation, and 6 (22.2%) patients who had normal glomerular function were still below -2 SDS at the last examination. Hypercalciuria was present in 25 (92.6%) patients at the first evaluation and in 6 (22.2%) patients at the last examination. The degree of NC worsened in 6 (22.2%), remained stable in 15 (55.5%) and decreased in 6 (22.2%) patients during the follow-up period. Chronic renal insufficiency (CRI) developed in 5 patients without there being any increase in the degree of NC.

In conclusion, growth and renal function in these patients generally depend on the nature of the underlying disease but not the degree of NC.

Key words: nephrocalcinosis, hypercalciuria, renal function, longitudinal growth, childhood.

Nephrocalcinosis (NC), defined as renal parenchymal calcification, occurs due to various metabolic or renal tubular disorders, vitamin D excess, medications, and prematurity. Systematic diagnostic evaluation in all children with NC should be done to elucidate the underlying cause and to preserve renal function with the initiation of specific therapy[1,2]. In this study, we aimed to analyze retrospectively the etiology of NC and to evaluate the results of follow-up of patients with NC.

Material and Methods

Forty-three children who were diagnosed with bilateral NC between November 1991 and January 2012 in our department were studied retrospectively. Two neonates treated with furosemide and five premature infants were excluded from the study. To assess long-term consequences, the data of 27 of the remaining 36 children who had a follow-up period of at least two years were examined in more detail. The records of patients were evaluated for age, sex, etiology of NC, clinical presentation, and follow-up period. Height standard deviation scores (hSDS) and glomerular filtration rate (GFR) were calculated at presentation and at the last examination. GFR was estimated using the Schwartz formula[3], and levels >90 ml/min/1.73 m^2 were considered as normal. In children younger than 1 year of age, age-specific limits for serum creatinine were used to evaluate renal function[4]. hSDS were calculated from published national standards[5]. The degree of NC and urinary calcium (Ca) excretion were recorded at presentation and at the last

examination. Hypercalciuria was defined as a urinary Ca excretion >4 mg/kg/day in collected samples or urinary Ca/creatinine ratio >0.8, >0.6, >0.4, and >0.2 mg/mg in children aged <6 months, 6 - 12 months, 1 - 2 years, and >2 years of age, respectively, in random urine samples.

Diagnosis of the underlying cause of NC was made as follows: distal renal tubular acidosis (dRTA) in patients with hyperchloremic metabolic acidosis, hypokalemia, hypercalciuria, high urine pH (>5.5), and positive urinary anion gap; Bartter syndrome in those with metabolic alkalosis, hypokalemia, and elevated urinary potassium and chloride excretion; vitamin D intoxication by hypercalcemia, low parathyroid hormone, high blood levels of 25 OH vitamin D, and a history of excess vitamin D intake; primary hypomagnesemia with hypercalciuria by hypomagnesemia, urinary magnesium wasting, and hypercalciuria; primary hyperoxaluria by molecular analysis; and Dent's disease in a male patient with hypercalciuria, low molecular weight proteinuria and bilateral medullary NC in addition to findings of proximal tubule dysfunction.

Alkali supplements with potassium citrate were given for the treatment of dRTA. Patients with idiopathic hypercalciuria (IH) and Dent's disease were administrated a low-sodium diet, potassium citrate and thiazide diuretics. Potassium supplementation and indomethacin were used for treatment of Bartter syndrome. Patients with vitamin D intoxication were given intravenous hydration, furosemide and prednisolone. Vitamin B6 was given for the treatment of hyperoxaluria.

The follow-up and diagnosis of NC in all children was made by ultrasonography performed by an experienced radiologist, and its evolution over time was evaluated retrospectively by the same radiologist according to pattern of echogenicity as follows[6]: A: a faint hyperechogenic rim around the sides and the tip of the pyramid, B: a more intense echogenic rim with echoes faintly filling the entire pyramid, C: intense echoes throughout the pyramid, and D: a solitary focus of echoes at the tip of the pyramid near the fornix.

All data are expressed as mean ± standard deviation and median (range) values. Wilcoxon signed rank test for nonparametric data was used to compare different operation times within each group. Analyses were performed with the Statistical Package for the Social Sciences (version 16.0 SPSS Inc., Chicago, USA) software, and $p<0.05$ was considered statistically significant.

Results

Diagnosis of 36 patients included 11 (30.5%) with distal renal tubular acidosis, 5 (13.8%) with Bartter syndrome, 3 (8.3%) with vitamin D intoxication, 2 (5.5%) each with IH, glycogen storage disease type I, and hyperoxaluria type 1, 1 (2.7%) each with Dent's disease, osteogenesis imperfecta, and familial hypomagnesemia with hypercalciuria, and 8 (22.2%) with unknown etiology. The most common condition leading to NC was hereditary tubulopathies, composed of dRTA, Bartter syndrome, Dent's disease, and familial hypomagnesemia with hypercalciuria, in 18 of 36 (50%) patients (Table I).

The most common signs and symptoms at presentation were growth retardation in 12 (41.4%) patients, polyuria-polydipsia in 5

Table I. Causes of Nephrocalcinosis in 36 Children

Condition	n (%)
Distal renal tubular acidosis	11 (30.5)
Bartter syndrome	5 (13.8)
Vitamin D intoxication	3 (8.3)
Idiopathic hypercalciuria	2 (5.5)
Glycogen storage disease type I	2 (5.5)
Hyperoxaluria type 1	2 (5.5)
Dent's disease	1 (2.7)
Osteogenesis imperfecta	1 (2.7)
Familial hypomagnesemia with hypercalciuria	1 (2.7)
Unknown	8 (22.2)
Total	36 (100)

Table II. Demographic, Clinical, Laboratory Features of Patients with Follow-Up >2 Years

Diagnosis Patient no/sex	Age (month)	Follow-up time (month)	↑Ca excretion initial	↑Ca excretion end	GFR* initial	GFR end	Degree of NC initial	Degree of NC end	hSDS initial	hSDS end
dRTA (n=10, 37%)										
1/F	196	30	+	-	45	55	D	C	-2.1	-1.8
2/M	216	209	+	-	-	120	C	D	-0.5	0.3
3/M	180	156	+	-	105	102	C	D	1.1	1.3
4/F	166	164	+	-	-	109	C	C	-2.1	-1.7
5/M	135	124	+	-	-	96	C	C	-2.2	0.1
6/M	131	129	+	-	-	119	C	B	-3.8	-1.2
7/M	137	114	+	-	127	134	C	D	-3.9	-0.9
8/F	90	81	+	-	-	85	D	D	-2.1	0.5
9/M	59	57	+	-	-	132	C	C	1.0	-0.5
10/F	150	147	+	-	-	92	D	D	-0.8	-2.2
Bartter syndrome (n=5, 18.5%)										
1/F	60	51	+	+	-	50	B	C	-2.8	-0.7
2/M	54	30	+	-	137	119	C	C	-1.2	-2.1
3/M	151	109	+	-	-	42	C	A	-2.2	-0.9
4/F	86	46	+	-	143	136	C	C	-1.9	-1.1
5/M	33	30	+	+	-	74	C	C	-3.6	-2.4
Vitamin D intoxication (n=3, 11.1%)										
1/F	83	71	+	-	112	125	C	C	-1.2	-1.0
2/F	52	47	+	-	-	110	C	C	-2.1	0.2
3/F	28	24	+	-	-	107	B	C	0.2	0.4
GSD type 1 (n=2, 7.4%)										
1/M	168	36	+	+	118	120	B	B	-2.1	0.5
2/M	211	30	+	+	122	118	B	B	-4.5	-5.1
Dent's disease (n=1, 3.7%)										
1/M	77	24	+	+	88	98	B	A	-0.9	-1.7
Idiopathic hypercalciuria (n=1, 3.7%)										
1/M	100	72	+	+	136	128	D	C	-1.3	-1.1
Unknown (n=5, 18.5%)										
1/F	168	72	-	-	115	112	C	C	1.3	0.6
2/F	118	26	+	-	134	133	C	C	-5.6	-7.4
3/M	112	46	+	-	96	112	C	D	-1.4	-1.3
4/M	78	24	-	-	130	120	C	C	0.9	1.5
5/M	75	71	+	-	-	110	B	A	-0.9	-3.8

↑: Elevated. F: Female. M: Male. GFR: Glomerular filtration rate (ml/min/1.73m^2). hSDS: Height standard deviation scores. GSDT 1: Glycogen storage disease type I. NC: Nephrocalcinosis

* GFR was not calculated in patients younger than 1 year at first presentation; creatinine values were within normal range according to age in these children.

(17.2%), and urinary tract infection and vomiting-dehydration in 3 (10%) each. NC was detected incidentally during the diagnostic procedures for genetic syndromes in 2 cases.

Of 27 patients who had more than two years of follow-up, 15 (55.6%) were boys. The median age at the first examination was 12 (range: 2-132) months and median follow-up time was 57 (range: 24-209) months. At presentation, GFR was <60 ml/min/1.73m^2 in only 1 patient with dRTA accompanied by sensorineural deafness and nephrolithiasis. During the follow-up period, 3 patients with Bartter syndrome and 1 with dRTA developed chronic renal insufficiency (CRI). Thirteen of 27 (48.1%) patients had hSDS <-2 at presentation; only 6 (22.2%) patients were still below -2 SDS at the last examination. Hypercalciuria was present in 25 (92.6%) patients at the first evaluation and in 6 (22.2%) patients at the last examination. The degree of NC worsened in 6 (22.2%), remained stable in 15 (55.5%) and decreased in 6 (22.2%).

Clinical, laboratory and anthropometric characteristics of the 27 patients are shown in Table II.

Distal RTA

Distal RTA was the most frequent condition associated with NC, found in 10 (33%) patients. Median follow-up time was 125 months (range: 30-209). Their hSDS improved from a median value -2.1 (range: -3.9/+1.0) to a median value of -0.7 (range: -2.2/+1.3) (p=0.09). Two patients developed CRI, 1 of whom had pattern D NC at first examination (Patient 8). The other one, who was not followed at any center for a long time, presented with renal failure and multiple renal stones; GFR mildly improved after stones were removed and NC improved from pattern D to pattern C during the follow-up (Patient 1) (Table II).

Bartter Syndrome

In 5 patients with antenatal Bartter syndrome, with a median follow-up time of 46 months (range: 30-109), hSDS increased from a median value of -2.2 (range: -3.6/-1.2) to -1.1 (range: -2.4/-0.7). Although there was no increase in the degree of NC, GFR of 3 patients was <80 ml/min/1.73m^2 at the end of the follow-up period, due to possible causes such as the use of indomethacin and hypokalemia in addition to NC.

Other Causes

In these patients, GFR remained in the normal range. Patient 2 with hypercalciuria, hyperoxaluria and skeletal dysplasia similar to achondroplasia and patient 5 with hypercalciuria, scoliosis and spinal segmentation abnormality associated with absence of the ribs localized to the mid-thoracic spine in the group of unknown etiology, 1 of the patients with glycogen storage disease type 1 and the patient with Dent's disease exhibited a decrease in hSDS at the end of the follow-up period. In other patients, hSDS demonstrated either no improvement or no change (Table II).

Discussion

The evolution and etiology of NC and whether it has any effect on growth parameters and renal function have been evaluated in limited studies[8,1,5]. Rönnefarth et al.[7] detected IH as the main cause of NC in 34% of 152 patients. However, in the other two studies, dRTA was the most common etiology, similar to our study[8,9].

In these studies, the clinical presentation of children with NC varied considerably; growth retardation or psychomotor delay was the most common manifestation[7-9]. In the multicenter German series[7], 41% and 32% of 72 children older than 1 year had heights < -2SDS at the first and last examination, respectively. In this study, significant growth improvement was seen only in patients with IH, whereas the patients with hereditary tubulopathy and vitamin D intoxication exhibited some degree of growth improvement. In the single-center Indian series[8], growth retardation continued in most patients at follow-up. Ammenti et al.[9] found that 54% and 22% of 28 patients had hSDS <-2 at the first and last investigation, respectively, in a multicenter study. In the current study, growth failure (hSDS <-2) existed in nearly half of the patients at presentation, half of whom improved with adequate therapies during the study period. The patients with hereditary tubulopathies, e.g. dRTA and Bartter syndrome, demonstrated mild to moderate growth improvement. It is notable that early and appropriate treatment may ensure growth

improvement in these tubulopathies, the two commonest causes of NC in the current study.

In our study, we found that GFR was <90 ml/min/1.73m^2 in 5 (18.5%) patients at the end of the study. In these patients, the degree of NC either decreased or was unchanged. CRI was probably associated with the underlying diseases, even though NC itself contributed to deterioration in renal function by causing interstitial and tubular damage. In the current study, the pattern of NC did not change in more than half of the patients (55.5%) during the follow-up and appeared not to affect growth and renal function. Rönnefarth et al.[7] found that the degree of NC remained the same in 43%, worsened in 41% and improved in 16% of the patients during the follow-up. In this study, the patients with hereditary tubulopathies and those with stage 3 NC were predisposed to advanced CRI, and 29% of patients had a GFR <80 ml/min/1.73 m^2. Mantan et al.[8] showed that the degree of NC was moderate to severe in 70% of patients, and CRI was observed in 17.5% of patients. Ammenti et al.[9] reported that NC worsened in 62%, remained stable in 30% and decreased in 8% of 26 patients, and persistence or even progression of NC did not have any effect on growth and renal function, similar to our study.

Hypercalciuria is considered as the most frequent predisposing factor for NC, accounting for 42-80%[7-9]. In our study, urinary Ca excretion was initially elevated in 92% of the patients. Although this ratio decreased to 22% at the last visit, this situation did not always accompany amelioration of NC. We suggest that inadequate fluid intake or ongoing hypocitraturia, hyperoxaluria, alkali urine, and poor compliance with medications may have contributed to progression of NC in these patients.

This study may have some limitations. In our study, we found that the most frequent condition of NC was hereditary tubulopathies. However, the patients with more serious illnesses such as dRTA might have applied to the hospital more frequently than the patients with other etiologies.

In conclusion, children with NC, which may be associated with different renal disorders, may present with various sign and symptoms. It seems that growth and renal function in these patients generally depends on the nature of the underlying disease. However, further studies with larger groups of children are needed to evaluate the effect of NC on renal function in the long term.

REFERENCES

1. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 2010; 25: 403-413.
2. Habbig S, Beck BB, Hoppe B. Nephrocalcinosis and urolithiasis in children. Kidney Int 2011; 80: 1278-1291.
3. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009; 20: 629-637.
4. Boer DP, de Rijke YB, Hop WC, Cransberg K, Dorresteijn EM. Reference values for serum creatinine in children younger than 1 year of age. Pediatr Nephrol 2010; 25: 2107-2113.
5. Neyzi O, Ertugrul T. Cocuk Sagligi ve Hastaliklari (Cilt 1). Istanbul: Nobel Kitabevi; 1989: 57–88.
6. Patriquin H, Robitaille P. Renal calcium deposition in children: sonographic demonstration of the Anderson-Carr progression. AJR Am J Roentgenol 1986; 146: 1253-1256.
7. Rönnefarth G, Misselwitz J. Nephrocalcinosis in children: a retrospective survey. Members of the Arbeitsgemeinschaft für pädiatrische Nephrologie. Pediatr Nephrol 2000; 14: 1016-1021.
8. Mantan M, Bagga A, Virdi VS, Menon S, Hari P. Etiology of nephrocalcinosis in northern Indian children. Pediatr Nephrol 2007; 22: 829-833.
9. Ammenti A, Pelizzoni A, Cecconi M, Molinari PP, Montini G. Nephrocalcinosis in children: a retrospective multi-centre study. Acta Paediatr 2009; 98: 1628-1631.