IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Microlithiasis and Nephrocalcinosis in Preterm Neonates. Is the Treatment Necessary? A One-Year Sonographic Follow-up Study

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ABSTRACT

Background: Renal microlithiasis includes renal hyperechogenic deposits in the calyces, pelvis, or ureter with a diameter of less than 2-3 mm by ultrasound. Currently, there is no information about the outcome and possible complications of renal calcification in premature infants in Iran. The current study aimed to evaluate its outcome in preterm infants.

Methods: A total of 50 preterm infants with microlithiasis and nephrocalcinosis enrolled in study. The follow-up ultrasound was evaluated 2, 6, and 12 months after diagnosis. Following the diagnosis, infants were assessed for nephrocalcinosis progression. The group was termed unrecovered if the issue persisted during follow-up, and it was considered recovered if it disappeared on follow-up ultrasound. The neonatal data included gestation age, birth weight, length of hospital stay, age at diagnosis of microlithiasis, and used medications.

Results: A total of 50 premature infants with microlithiasis and nephrocalcinosis, including 14 females (28%) and 36 males (72%), were born with an average gestation week of 30.78 ± 2.78. The mean age of diagnosis was 2.60 ± 1.11 months. The average hospital stays at the neonatal intensive care unit (NICU) and neonatal ward were 27.38 ± 16.06 and 10.50 ± 9.57 days, respectively. At the end of the 12-month study period, renal calcification recovered in 40 (80%) patients. There was no significant difference between the two groups of patients with sustained and recovered microlithiasis in terms of gender, age of onset of renal calcification, gestational age, mean hospital stay in NICU and neonatal ward, use of antibiotics, potassium citrate, and hydrochlorothiazide. A p-value of less than 0.05 was considered statistically significant for all statistical analyses.

Conclusion: The obtained results of the study reveal that a high percentage of premature infants with nephrocalcinosis recovered at the end of the 12-month period, indicating this phenomenon is benign.

Keywords: Aminophylline, Kidney function, Microlithiasis, Nephrocalcinosis, Premature infants

Introduction

Renal microlithiasis is defined as the ultrasonographic identification of hyperechogenic deposits in the renal calyces, pelvis, or ureter less than 2-3 mm in diameter. Renal calyceal microlithiasis is a condition in which deposits are only found in the calyces. In 1982, Hufnagle et al. (1) described nephrocalcinosis in premature newborns treated with long-term furosemide. Nephrocalcinosis refers to calcium deposition in the renal parenchyma and preterm neonates develop as a result of an imbalance between stone-promoting and stone-inhibiting components. La

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Please cite this paper as:
Mostafa-Gharehbaghi M, Mortazavi F, Hosseinzadeh Asl H, Bagheri Gahvechi I, Parizad R, Jafarisis S, Masoumi S. Microlithiasis and Nephrocalcinosis in Preterm Neonates. Is the Treatment Necessary? A One-Year Sonographic Follow-up Study. Iranian Journal of Neonatology. 2023 Jul: 14(3). DOI: 10.22038/IJN.2023.69771.2350

Mannaet et al. (2) described calyceal microlithiasis for the first time in 196 children whose renal ultrasonography identified hyperechogenic spots < 3 mm in diameter.

Monet-Didailler et al. (3) reported 10 cases of term neonates initially diagnosed as nephrocalcinosis, but follow-up ultrasound after 2 weeks showed complete recovery in all patients except one. The researchers suspected that the initial diagnosis was due to medullary hyper-echogenicity that mimicked nephrocalcinosis. This suggests that neonatal nephrocalcinosis is often a transient condition, resolving spontaneously in approximately 75% of neonates. There is growing evidence of a link between low birth weight and low nephron numbers and an increased risk of adult cardiovascular disease and renal insufficiency (4). Recent research has insufficiently supported the idea that low birth weight is associated with impaired kidney function, at least not until 20-26 years; therefore, a complete consensus is still to be reached. However, the formation of renal calcification in prematurely born children can compromise renal function later in life (5).

Microlithiasis and nephrocalcinosis in infants and children differ from that in adults regarding epidemiology, etiology, symptoms, indicators, imaging modalities, and therapy (6). Compared to adults, renal stones in children should not be neglected due to the severe morbidity and greater recurrence rate. Since most infants and children with renal stones have metabolic origins, a diagnostic examination is required for every pediatric patient with the first recorded renal stone to identify the underlying metabolic problems that might cause recurrent urolithiasis (7,8). Renal stone formation in infants and children is often a multifactorial disorder involving various underlying diseases and disorders, such as heredity, ethnicity, climate, and dietary habits (9).

Microlithiasis can cause pain, infection, and kidney damage, leading to renal failure in severe cases. Bladder stones affect less than 10 percent of children in North America. It is also common in other regions due to dietary and other factors. In 11-24 percent of children, anatomic anomalies, such as ureteropelvic junction (UPJ) obstruction or ureterovesical junction (UVJ) obstruction are discovered during a microlithiasis work-up (10).

In the adult population, there is a significant male majority, but this gender imbalance is less evident in children. Recent research has indicated a roughly equal gender distribution or even a female predominance among pediatric stone cases. While microlithiasis can develop at any age in children, infants represent around 20% of all pediatric stone cases and have different histories and presentations (11,12).

Currently, there is no information about the outcome of renal calcification in premature infants in our country. The current study evaluated the outcome of microlithiasis in preterm infants weighing less than 1500 grams.

Methods

In this cross-sectional study, 50 premature infants with a birth weight under 1500 g or a gestation age less than 35 weeks were included. The infants were admitted to the neonatal ward (general care unit that provides medical care to newborns who do not require intensive care) and the neonatal intensive care unit (NICU), a specialized unit designed to provide care to critically ill newborns, premature or with serious health problems which have advanced medical equipment and staffed by trained neonatologists and nurses at Al-Zahra and Tabriz Children Hospitals with microlithiasis and nephrocalcinosis in renal ultrasound. The excluded infants were those with major congenital anomalies, lack of cooperation or parental consent to follow-up, term infants with microlithiasis, incomplete data, and dead before the performance of follow-up ultrasonography.

All renal ultrasonography was performed using the Sonix-OP machine (linear- L14-5MHz and micro convex-C9-5/10MHz probes) transducers during the study period by an expert pediatric radiologist. Nephrocalcinosis is considered a hyperechogenic deposit in the renal parenchyma. Microlithiasis was defined as hyperechogenic spots <3 mm in diameter in renal calyces or pelvis.

Following a microlithiasis diagnosis, infants were monitored for a year. At 6 and 12 months of age, ultrasounds were performed to assess the microlithiasis progress of patients. Nephrocalcinosis was termed unrecovered if it persisted during follow-up and was considered recovered if it disappeared on follow-up ultrasound. Data on neonatal period, including birth weight, length of hospital stay, age at diagnosis of microlithiasis, used medications, nutritional status, and the type of treatment received for microlithiasis were recorded. All patients underwent the laboratory tests of complete blood count, urinalysis and urine culture, blood test for urea, creatinine, sodium, potassium, calcium, phosphate, uric acid, and bicarbonate level. In suspected renal tubular

acidosis (RTA) cases, serum chloride and blood pH were tested. Random urine samples were obtained to measure calcium, creatinine, citrate, acid uric, and oxalate.

Statistical analyses were performed using the statistical package for social sciences (SPSS) version 16. Quantitative data were presented as mean ± standard deviation (SD), and qualitative data as frequency and percent. Independent t-test used for testing continuous normally distributed data. Categorical data were compared between groups using the Chi-square or Fisher exact test. Two-tailed tests were used, and a p-value of less than 0.05 was considered statistically significant.

Ethical approval

The investigation conformed with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review board (ethics committee for research of the Tabriz University of Medical Science - reference number: IR.TBZMED.REC.1398.786).

Results

A total of 265 preterm infants with renal ultra-sonographic examination were enrolled to study, among whom 50 infants with microlithiasis and nephrocalcinosis were studied. The findings indicated that 14 female neonates (28%) and 36 male neonates (72%) had microlithiasis. The neonates with microlithiasis had an average gestation age of 30.78 ±2.78 weeks. The mean age of diagnosis of neonatal microlithiasis was 2.60 ± 1.11 months. Table 1 shows the status of renal involvement by examination time and kidney involvement. Microlithiasis and nephrocalcinosis were present in 28 (56%) infants at 6 months and 10 (20%) cases at 12 months after birth. Therefore, 40 (80%) infants resolved stones at the end of 12 months (Table 1).

Among the recovered infants, 27 (65.5%) were boys. Of non-recovered infants, nine (90%) were boys, and 1 (10%) was a girl, but there was no significant difference between the two groups in terms of gender (p = 0.15). The diagnosis age of microlithiasis and nephrocalcinosis was 2.64 ± 1.10 and 2.43 ± 1.20 months in the recovered and non-recovered groups, respectively, without any significant difference (p = 0.63). Furthermore, microlithiasis resolved at the age of 12 months in two patients with conservative therapy (Table 1).

There was no significant difference between the two groups of infants in laboratory tests (Table 2).

Neonates whose microlithiasis resolved at month 12 were born at 30.62 ± 2.78 weeks of gestation, compared to 28.3 ± 0.40 weeks for neonates with unresolved microlithiasis at the end of the study period. However, the two groups had no statistically significant difference (p = 0.44). The studied neonates were admitted to the NICU at 27.38 ± 16.06 days and to the neonatal ward at 10.50 ± 4.57 days. Neonates with resolved microlithiasis were admitted to the NICU for an average of 29.15 ±15.77 days and 11.02 ±1.50 days in the neonatal ward. Infants with unresolved microlithiasis were hospitalized in the NICU for 20.02 ± 7.16 days and 8.40 ± 3.86 days in the neonatal ward without any significant difference (p = 0.06 and p = 0.44, respectively).

The family history of renal stones was negative

Table 1. The sonographic findings in two groups for resolving nephrolithiasis

			Unrecovered patients	Recovered patients	All patients	P value
2nd Month	Number of Stones (min-max)		2 - 15	1 - 12	1 - 15	0.31
	Max Size (mm)		0.81±2.37	0.79±2.11	0.80±2.16	0.36
	Kidney involvement	Bilateral	7(70%)	29(72.5%)	36(72%)	0.62
		Unilateral	3(30%)	11(27.5%)	14(285)	
6th Month	Number of Stones (min-max)		7 - 1	0 - 10	0 - 10	0.001
	Max Size (mm)		0.49±1.91	0.62±1.78	0.57±1.82	0.58
	Kidney involvement	Bilateral	7(70%)	8(20%)	15(30%)	0.003
		Unilateral	3(30%)	10(25%)	13(26%)	
		No involvement	0(0%)	22(55%)	22(44%)	
12th Month	Number of Stones (min-max)		1 - 3	0	0 - 3	0
	Max Size (mm)		0.52±1.56	0	0.52±1.56	0
	Kidney involvement	Bilateral	2(20%)	0	2(4%)	0.001
		Unilateral	8(80%)	0	8(16%)	
		No involvement	0(0%)	40(100%)	40(80%)	

Table 2. Laboratory tests in studied patients

	Unrecovered patients	Recovered patients	All Patients	P value
Urine Calcium (mg/dl)	2.01±8.44	1.59±8.03	1.67±8.11	0.68
Blood Calcium (mg/dl)	0.61±9.84	1.55±9.88	1.14±9.87	0.25
Blood Uric acid (mg/dl)	0.33±2.68	0.35±2.64	0.34±2.64	0.74
Urine Cr (mg/dl)	3.72±20.55	7.65±21.15	7.01±21.03	0.81
Urine Citrate (mg/dl)	1.02±2.46	0.89±2.28	0.91±2.32	0.66
Urine Oxalate (mg/dl)	0.095±0.183	0.062±0.183	0.069±0.183	0.99
Uric acid/Cr	0.031±0.134	0.041±0.133	0.033±0.133	0.82
Urine Citrate/Cr	0.041±0.118	0.044±0.122	0.043±0.133	0.71
Urine Oxalate/Cr	0.008±0.011	0.005±0.010	0.006±0.010	0.62
Urine Calcium /Cr	0.061±0.408	0.143±0.409	0.130±0.409	0.97

in 95% of the studied patients (Table 3).

Of the recovered infants, 29 (72.5%) received antibiotics, 18 (45%) diuretics (hydrochlorothiazide), and 28 (71.8%) aminophylline. Among the unrecovered infants, 5 (50%) received antibiotics, 6 (60%) diuretics (hydrochlorothiazide), and 4 (40%) aminophylline. Regarding medication therapy between the two groups, Aminophylline significantly improved nephrocalcinosis.

Table 3. Demographic information of patients

		Unrecovered	Recovered	All patents	P value
Gender	Female	1(10%)	13(32.5%)	14(28%)	0.156
	Male	9(90%)	27(67.5%)	36(72%)	
Gestational age at birth(week)		31.40 ± 2.83	30.62 ± 2.78	30.78 ± 2.78	0.440
Age at diagnosis of microlithiasis (months)		2.43± 1.20	2.64 ± 1.10	2.60 ± 1.11	0.638
weight (gram)		1408.00±144.05	1301.62±220.14	1322.90±210.31	0.155
Aminophylline		4(40%)	28(71.8%)	32(64%)	0.04
Antibiotic		5(50%)	29(725%)	34(68%)	0.17
Diagnosis in addition to prematurity	TTN	0(0%)	1(2.5%)	1(2%)	0.019
	Jaundice	2(20%)	0(0%)	2(4%)	
	Pneumonia	1(10%)	0(0%)	1(2%)	
	IVH	0(0%)	3(7.5%)	3(6%)	
Hospitalization period	NICU	20.30 ± 16.02	29.15 ± 15.77	27.38 ± 16.06	0.062
	Ward	8.40 ± 3.86	11.02 ± 10.50	10.50 ± 9.57	0.444

TTN: Transient tachypnea of the newborn, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit

Discussion

According to the study findings, almost half of premature infants showed improvement after 6 months based on imaging, and approximately three-quarters of infants improved after a year. The findings of the current study indicated the benign course of nephrocalcinosis and microlithiasis in preterm infants. In a study by Lee et al. (13), serum sodium on day 1, serum creatinine and fractional excretion of calcium at weeks 1 and 2, and serum calcium, fractional excretion of sodium, and urine Na on week 2 of life were significantly different between the neonates with nephrocalcinosis and infants in the control group. The nephrocalcinosis group showed significantly higher serum creatinine, fractional excretion of sodium and calcium than the control group, suggesting a greater decrease in renal function in these patients. The abnormal laboratory findings vanished 4 and 8 weeks after birth in infants with nephrocalcinosis. Porter et al.(14) found that 75 percent of children with nephrocalcinosis were resolved after a median follow-up of 6.69 years, which might be attributed to the limited cases of children with a history of nephrocalcinosis in their research. However, a significant number of patients with nephrocalcinosis recovered in general, and there was no difference in urine biochemistry between the two groups of nephrocalcinosis and control as the current study indicated (15). In a study by Saarela et al. (16), more than one-third of preterm infants with nephrocalcinosis improved by 6 months of age, but overall by age 6 years, only about 10% of children had nephrocalcinosis.

The other studies reported 62 patients (61% male) with stones or nephrocalcinosis diagnosed at a median age of 2.9 months. Thirty-seven percent had a history of admission to the NICU because of prematurity, low birth weight, or comorbidities. Ultimately, surgical intervention was required in seven patients. Stone size was a

predictor of the eventual need for surgical intervention. Among patients not requiring surgical intervention (n = 38), the estimated median time to spontaneous resolution of urolithiasis was 1.1 years (95% CI 0.89–1.53, range two months–6 years) and 1.2 years for nephrocalcinosis (95% CI 0.59–2.13). They concluded that newborns and infants diagnosed with urolithiasis and nephrocalcinosis in the first year of life had a high likelihood of spontaneous resolution (17,18).

In the present study, the size of the renal microlithiasis at 2 and 6 months was lower in the recovered group, compared to the unrecovered group, suggesting reducing the size of the stones may provide these patients with long-term benefits. Therefore, it is possible to determine the size of the stones for selecting an approach to treatment and predicting the short-term prognosis by serially examining the patients. At the end of the study, there was no significant difference between recovered and unrecovered infants in terms of blood calcium, uric acid to creatinine ratio, urinary citrate to creatinine, urinary oxalate to creatinine, and urinary calcium to creatinine in the laboratory tests. These laboratory tests may not be appropriate in evaluating the outcome of nephrolithiasis. In a 6-year study period on 525 preterm infants, approximately one showed kidney dysfunction. The mean gestation age and birth weight of infants who developed microlithiasis were 27.5 (26–29.1) weeks and 980 (760–1128) grams, compared with 27.7 (26.4–29.1) weeks, p= 0.88 and 900 (760–1140), p=0.74 in infants without microlithiasis (19). Similar to the current study, after discharge, nephrocalcinosis resolved 12-18 months after the diagnosis in about two infants out of three (61%) in a study by Fayard et al. (15). In contrast to the present study, 50 percent of cases of nephrocalcinosis were discovered at four weeks of life in the study by Lee et al. (13), while the remainder were detected at eight weeks of life and the average length of stay of 75 days (215-48: 95th percentile-5th), which may be due to lower gestational age in the infants of their study.

In 85% of infants, the resolution of nephrocalcinosis occurs in the first years of life (20). Although the spontaneous resolution of nephrocalcinosis occurs in most children, some are at risk of renal damage later in life, validating its screening for preterm neonates (19). Nephrocalcinosis resolved in 60% of preterm babies followed up at 1-2 years of age, and another study found resolution in 44% and improvement in 56% of very low birth weight preterm babies at 21.3 months of age (21,22), which confirms the findings of the present research. In addition, children with chronic pulmonary illness and resistant compensated respiratory acidosis showed extended nephrocalcinosis (20). According to reports, children with vesicoureteral reflux (VUR) are more likely to have recurrent urinary tract infection (UTI), and the accumulation of calcium salts in the urine due to the urine's stagnation in collecting tubules may lead to nephrocalcinosis (23,24). There is a controversy about the ideal management of nephrocalcinosis in newborns. A conservative approach is recommended in less than 5 mm, and surgical intervention is advised in urine flow obstruction or failed conventional therapy (25). There are different results in follow-up studies. Some studies suggest that microlithiasis does not indicate an increased risk of lithiasis. In contrast, in some reports, approximately one-third of the involved patients may develop more giant stones on long-term follow-up (25,26).

In the current study, there was a correlation between severe morbidity and the incidence of nephrocalcinosis in the most immature preterm children. These infants, who require more intensive treatment such as extended invasive care, postnatal steroids, and diuretics for the management of bronchopulmonary dysplasia (BPD), tend to have a higher risk of developing nephrocalcinosis (27, 28). This supports This finding aligns with the results of Chang et al.'s (6) multivariate analysis, which identified comorbidities as independent risk factors for nephrocalcinosis (6,23).

It is important to acknowledge the limitations of the present study, including the small sample size and short-term follow-up period. o obtain more robust and comprehensive results, future multicenter studies with larger sample sizes and long-term follow-up are recommended.

Conclusion

In conclusion, the findings of this study indicate that a significant proportion of preterm infants with microlithiasis experience recovery over a 12-month period, suggesting a benign condition. The recovered neonates and the group who still had nephrocalcinosis after 12 months did not show significant differences in terms of gender, diagnosis age, gestational age, or duration of stay in the neonatal intensive care unit or neonatal ward. There was no significant difference

in laboratory tests between the two groups. Although aminophylline was the only medication that can accelerate nephrocalcinosis recovery in the current study, a dedicated study is needed for a more detailed investigation and conclusion.

Acknowledgments

This study was supported by Pediatric Health Research Center. The researchers express their deepest gratitude to all the parents and the staff of the neonatal department of the hospital for their cooperation in conducting this research.

Conflicts of interest

The authors have no conflict of interest to report.

Funding

None.

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