Nephrocalcinosis in Very Low Birth Weight Infants: A Single Center Experience

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Objectives : *To determine the incidence and risk factors of nephrocalcinosis in very low birth weight infants.*
Material and Method : *Medical records of inborn infants with gestational age less than 32 weeks or birth weight less than 1,250 grams were collected and analyzed. All infants were born at King Chulalongkorn Memorial Hospital in the year 2003. At least one renal ultrasonographic scan was performed on every infant as a routine screening before discharge. Data on family history of renal stone, gestational age, birthweight, infant's illness, fluid intake during the first 6 weeks of life, duration of respiratory support, medications, serum calcium, phosphate and alkaline phosphatase level, duration of parenteral nutrition, length of hospitalization, ultrasonographic findings and related renal morbidity were collected and compared between the groups of infants with and without nephrocalcinosis.*
Results : *Thirty six infants were included in the present study. Fourteen had abnormal ultrasound scans compatible with nephrocalcinosis giving an overall incidence of 38.9%. Factors associated with nephrocalcinosis included severity of respiratory illness, PDA, oxygen dependency, furosemide therapy, and fluid restriction. Urinary tract infection was the renal morbidity found in 3 infants (21.4%). Nephrocalcinosis was resolved in one out of 7 infants who had repeated renal ultrasound scan at about 2 months after the first scan.*
Conclusion : *Very low birth weight, preterm infants have a risk of developing nephrocalcinosis especially those with severe respiratory illness and prolonged use of furosemide. Infants at risk should be screened with renal ultrasonography prior to discharge from the hospital.*

Keywords : *Nephrocalcinosis, Very low birth weight infant, Renal ultrasound scan, Urinary tract infection, Furosemide*

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Nephrocalcinosis in preterm infants was first described in 1982 by Hufnagle *et al*, who attributed the cause primarily to furosemide treatment [1]. Since then there have been many reports published in the international literature. The incidence varied from 20% [2,3] to 64% [4] in very low birth weight (VLBW) infants. The first reports linked nephrocalcinosis with hypercalciuria and furosemide administration while current evidence suggests a multifactorial pathogenesis. The vulnerability of extreme immaturity and underdevelopment of renal function may also be the important variable factors for pathogenesis. Other risk factors that may contribute towards nephrocalcinosis include fluid restriction, parenteral nutrition, long-term ventilation, prolonged immobility, bone demineralization, and some other medications (e.g., xanthines, dexamethasone), all of which are common in sick preterm infants [5,6].

However, studies on incidence and risk factors of nephrocalcinosis in VLBW infants in Thailand are scarce. The authors, therefore examined the incidence and possible contributory factors towards nephrocalcinosis in our population of preterm infants (< 32 weeks gestation) with weights less than 1,250 grams.

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Material and Method

The authors analyzed all available medical records of preterm infants of less than 32 weeks gestation or with a birth weight of less than 1,250 grams who were admitted to the neonatal intensive care unit at King Chulalongkorn Memorial Hospital from January to December 2003. Infants born with major congenital anomalies or those who died before discharge were excluded. They were searched for following data: family history of renal stone, gestational age, route of delivery, Apgar score, birth weight, infant's illness, fluid intake during the first 6 weeks of life, duration of respiratory support, medications, serum calcium, phosphate and alkaline phosphatase level, urine examination, duration of parenteral nutrition, length of hospitaliza-

tion, ultrasonographic findings and related renal morbidity. A renal ultrasound scan was performed on all enrolled infants once before discharge as routine screening protocol by a neonatology fellow. When nephrocalcinosis was suspected, the diagnosis was confirmed by a scan performed by pediatric radiologists.

Statistical Method

The groups of infants with and without nephrocalcinosis were compared using appropriate two sample techniques by SPSS version 8.0 Software (SPSS, Chicago, IL). Student t-test was used to compare average levels of continuous variables. Because of the considerable skewness shown by many data, the Mann-Whitney U test was used as appropriate. The χ^2 test of association was used to analyze binary variables, augmented by Fischer's Exact Test when expected frequencies were too small to justify the χ^2 approximation. Individual tests were taken to be significant when $p < 0.05$.

Results

Between January 2003 and December 2003, there were 36 preterm infants who fulfilled the inclusion criteria. Of these, 14 infants were diagnosed with nephrocalcinosis. The incidence of nephrocalcinosis was 38.9% among the preterm infants with a birth weight less than 1,250 g.

Basic data

Gestational age, birth weight, sex and growth retardation were not significantly associated with an increased risk of nephrocalcinosis (Table 1). No family history of renal stone was detected in all infants.

Infant's illness before diagnosis of nephrocalcinosis

Nearly all infants in both groups were diagnosed with respiratory distress syndrome (RDS). The infants who developed air leak syndrome, renal failure and symptomatic PDA and who underwent surgical ligation were significantly associated with an increased risk of nephrocalcinosis. Although, PDA was rather common in these infants, it's association was not statistically significant *($p = 0.054$)*. Five out of 14 infants with nephrocalcinosis developed acute renal failure which occurred within 5 days of age. This was due to the side effect of indomethacin. However, all of them fully recovered. None of the infants without nephrocalcinosis had renal failure. Concomitant illness such as pulmonary hemorrhage, necrotizing enterocolitis (NEC), apnea of prematurity and sepsis were not significantly different between both groups (Table 2).

Ventilation and oxygen dependency

The infants with nephrocalcinosis seemed to require longer duration of mechanical ventilation than those without nephrocalcinosis, but this finding was not statistically significant ($p = 0.089$). Duration of nasal continuous positive airway pressure (NCPAP) and re-intubation requirement were also not significantly different between the two groups. The median duration of oxygen dependency for infants with nephrocalcinosis was 36.5 days compared with 5 days for those without. Ten (71.4%) infants with nephrocalcinosis were oxygen dependent at 36 weeks postconceptional age compared with 3 (13.6%) of those without.

Medication

Nephrocalcinosis was not associated with either surfactant therapy, pre or postnatal steroid or

Table 1. Basic data of the infants with or without nephrocalcinosis

	With (n = 14)	Without (n = 22)	P-value#
Gestational age (weeks), (Mean ± SD)	28.1±1.4	28.4±1.4	0.99
Birth weight (g), (Mean ± SD)	1,025±156.1	995.0±145.6	0.83
Male sex (%)	71.4	54.5	0.61
SGA (%)	7.1	18.2	0.28

Values are mean ± standard deviation
SGA = Small for gestational age or intrauturine growth retardation, # = not statistical significance

Table 2. Infant's illness before diagnosis of nephrocalcinosis

	With (n = 14)	Without (n = 22)	P-value
RDS	14 (100)	20 (90.9)	0.84
Pulmonary hemorrhage	2 (14.3)	1 (4.5)	0.12
Air leak syndrome	5 (35.7)	1 (4.5)	0.02*
PDA	13 (92.9)	13 (59.1)	0.054
-PDA underwent surgical ligation	4 (30.8)	0 (0)	0.035*
Renal failure	5 (35.7)	0 (0)	0.005*
Sepsis	11 (78.6)	11 (50)	0.65
NEC	6 (42.9)	5 (22.7)	0.22
Apnea of prematurity	13 (92.9)	21 (95.5)	0.92

Values in parentheses are percentages
RDS = Respiratory distress syndrome, PDA = Patent ductus arteriosus, NEC = Necrotizing enterocolitis, * = Statistical significance

aminophylline treatment (Table 4). However, it was significantly associated with furosemide treatment. The mean total dosage of furosemide given to infants with nephrocalcinosis before ultrasound scan detection was 102.2 ± 118.2 mg and in those without was 32.3 ± 81.1 mg. The median duration of furosemide usage in infants with nephrocalcinosis before diagnosis was also significantly longer than those without (39 days vs 7 days; $p = 0.001$). Usage of aminoglycosides, indomethacin, amphotericin, all of these were not associated with an increased risk of nephrocalcinosis.

Fluid intake and nutrition

Infants with nephrocalcinosis had a lower mean fluid intake from 1-6 weeks of life, but these were only statistically significant during week 5 and week 6 (Fig. 1). The median duration of total parenteral nutrition (TPN) of infants with and without nephrocalcinosis were 18.5 and 15.5 days respectively ($p = 0.436$). Age at full enteral feeding was also not significantly different in both groups (median age in nephrocalcinosis group and those without were 41 and 30 days respectively; $p = 0.158$).

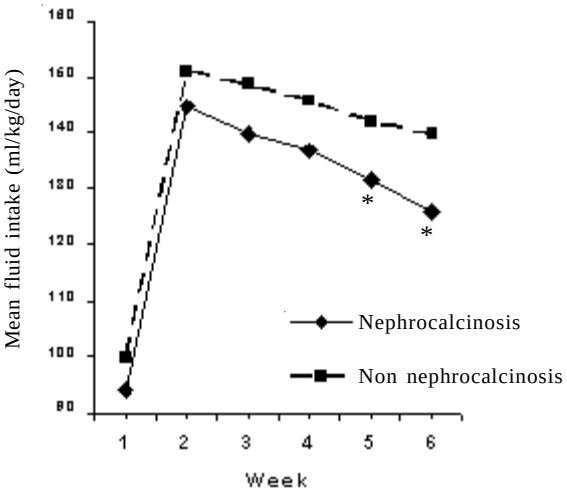

Fig. 1 Mean fluid intake for the first 6 weeks of life in infants with nephrocalcinosis and those without
* = significant difference

Table 3. Respiratory support

	With (n = 14)	Without (n = 22)	P-value
Mean ± SD duration of mechanical ventilation (days)	23.9+24.4 (range 0-69)	8.3+12.4 (range 0-51)	0.09
Mean ± SD duration of NCPAP (days)	17.1+15.6 (range 1-60)	14.6+13.3 (range 0-49)	0.60
Re-intubation, ≥ 2 episodes	3 (27.3)	6 (37.5)	0.76
Oxygen (median days)	36.5	5	0.009*
O_2 dependent at 36 wks PCA	10 (71.4)	3 (13.6)	0.001*

Values in parentheses are percentages
NCPAP = Nasal continuous positive airway pressure; PCA = Postconceptional age; * = Statistical significance

Table 4. Relation between medication and nephrocalcinosis

	With (n = 14)	Without (n = 22)	P-value
Antenatal steroid	5 (35.7)	14 (63.6)	0.27
Postnatal steroid	2 (14.3)	1 (4.5)	0.10
Surfactant therapy	10 (71.4)	9 (40.9)	0.48
Aminophylline	13 (92.9)	21 (95.5)	0.86
Furosemide			
Mean ± SD total dosage (mg)	102.2±118.2	32.3±81.1	0.001*
Mean ± SD duration (days)	38.0±25.8	12.5±19.3	0.001*
Aminoglycoside	13 (92.9)	20 (90.9)	0.82
Indomethacin	7 (50.0)	8 (36.4)	0.67
Amphotericin	5 (35.7)	4 (18.2)	0.53

Values in parentheses are percentages
* = Statistical significance

Serum biochemistry

Serum calcium, phosphate, and alkaline phosphatase level were not significantly different in both groups. Mean serum calcium, phosphate, and alkaline phosphatase level in infants with and without nephrocalcinosis were 9.5 ± 0.9 vs 9.2 ± 0.8 mg/dl, 5.1 ± 1.3 vs 5.7 ± 1.2 mg/dl and 302.2 ± 86.8 vs 265.7 ± 89.4 U/L respectively.

Ultrasound findings

The mean age of diagnosis of nephrocalcinosis was 68.1 days or 38 weeks post conceptional age. Nephrocalcinosis were found only in the left kidney of 4 infants while the other 10 infants had it in both sides. Ultrasonographic findings demonstrated hyperechogenicity at pyramids in 5 infants (35.7%), at medullary area in 8 infants (57.2%), and pelvic stone in 1 infant (7.1%). No other abnormalities of urinary system or other pelvic organs were detected.

Only 7 (50%) infants with nephrocalcinosis had follow-up ultrasound scan. The mean time after the first scan was 7.6 weeks. Four infants (57.1%) had no improvement, and 2 (28.6%) were partially improved.

Only one infant (14.3%) had regression to normal renal scan findings.

Related renal morbidities

Three (21.4%) infants with nephrocalcinosis developed urinary tract infection before discharge from the hospital. All urine culture grew *E. coli*. There were no hypertension, hematuria, or abnormal creatinine level found before discharge. The median day of hospitalization of the infants with nephrocalcinosis was 110.5 days compared with 71 days of those without ($p = 0.002$).

Discussion

The incidence of nephrocalcinosis (38.9%) in the present study is not different from the previous reports [2-4]. Gestational age and birth weight are not associated with an increased risk of nephrocalcinosis, which are similar to the findings of Ezzedeen at al [8] but they are different from other studies [4,7,9]. This discrepancy may reflect the fact that immaturity is not the only factor of nephrocalcinosis. Murphy and Mendosa reported that preterm infants with lung disease had decreased urinary citrate[10]. It may predispose them to nephrocalcinosis, because citrate is a known inhibitor of renal calcification in adults and children [5,11]. Although the authors did not measure urine citrate level, the infants with nephrocalcinosis in the present study might have lower level than those without.

Ezzedeen *et al* [8] hypothesized that there may be a vulnerable time during which even transient presence of several risk factors could lead to renal calcification. Severe respiratory illness, as indicated by the incidence of air leak syndrome, duration of oxygen therapy and oxygen dependence at 36 weeks postconceptional age, is significantly associated with nephrocalcinosis in the presented infants which is in agreement with other studies [3,7]. The authors also found that severity of PDA and transient renal failure in the early days of life (due to indomethacin treatment) were associated with nephrocalcinosis. Chronic lung disease, PDA and renal failure also lead to prolonged fluid restriction and usage of furosemide, both are risk factors of nephrocalcinosis [5,7,8,11].

Formation of nephrocalcinosis following furosemide administration can be explained by the drug reaction on the kidney. Furosemide inhibits active chloride reabsorption in the thick ascending limb of Henle's loop, thus, preventing the passive reabsorption of calcium and resulting in hypercalciuria. Renal magnesium wasting from furosemide effect may play the role of stone formation because magnesium is an inhibitor of crystal formation[5]. However, studies on the association between furosemide usage and nephrocalcinosis in low birth weight infants were controversial. The first report by Hufnagle *et al* [1] and others [2,4,8,12] confirmed this association but the study of Short and Cooke [3], and the work of Narendra *et al* [7] did not significantly show such association. The latter authors hypothesized that furosemide was prescribed for infants who were already at risk of nephrocalcinosis because of other factors such as severe respiratory disease.

Fluid restriction and prolonged TPN are other predisposing factors of nephrocalcinosis [6]. The authors found only fluid restriction in week 5 and week 6 were associated with nephrocalcinosis. TPN duration was not significantly different between both groups in the present study. Although, studies of Short and Cooke [3] and Hoppe *et al* [9] found association between nephrocalcinosis and duration of TPN.

Very low birth weight infants receiving parenteral nutrition may develop elevated urinary oxalate concentrations via metabolism of ascorbate and glycine in parenteral solution and this hyperoxaluria may contribute to stone formation [5,11]. The authors did not show the data of calcium and phosphate intake in the present study because all the infants in the intensive care unit received the same nutritional protocol.

Ultrasonographic findings in the present study is similar to previous reports [7,9,13]. Nephrocalcinosis is more commonly found in both kidneys and the common site of lesions are in the medullar and pyramids. Long term outcome of nephrocalcinosis is not clearly defined. Nephrocalcinosis resolved in one out of 7 infants who had repeated renal ultrasound scan at approximately 2 months after the first scan. Pope et al reported that nephrocalcinosis resolved in approximately 50% of the patients 5 to 6 months after discontinuation of furosemide. The only factor that appeared to be the prediction of the infant who would have resolution was the urinary calcium-to- creatinine ratio when nephrocalcinosis was diagnosed[14]. Saarela et al have also demonstrated that in about half of the affected infants, renal change was transient. In infants with extensive nephrocalcinosis, their condition still persisted at 5-6 years of age [2]. Persistent nephrocalcinosis and continuous use of furosemide are associated with high renal morbidity, including decreased renal growth, decreased glomerular function, renal tubular dysfunction, urinary tract obstruction, hematuria and increased risk of urinary tract infection [11]. Only three out of 14 infants (21.4%) with nephrocalci-

nosis developed urinary tract infection during hospitalization. This may be under estimated because only the symptomatic infants were investigated for possible urinary tract infection.

Conclusion

The authors have documented an incidence of nephrocalcinosis of 38.9% in very low birth weight infants (<1250 grams). It was particularly associated with severe respiratory illness and prolonged use of furosemide. Transient renal failure, severe PDA and fluid restriction were also risk factors. Infants at risk should be screened at term or prior to discharge from the hospital with renal ultrasound scan. However, the long term outcome of nephrocalcinosis still needs clarification.

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ภาวะแคลเซียมเกาะเนื้อไตในทารกแรกเกิดน้ำหนักน้อยมาก ประสบการณ์ในโรงพยาบาลแห่งหนึ่ง

กฤช เกตุแก้ว, พิมลรัตน์ ไทยธรรมยานนท์, สันติ ปุณณะหิตานนท์

ได้ทำการศึกษาย้อนหลังในทารกเกิดก่อนกำหนดน้ำหนักน้อยมากที่โรงพยาบาลจุฬาลงกรณ์ในปี พ.ศ.2546 เพื่อศึกษาอุบัติการณ์และปัจจัยที่เกี่ยวข้องกับการเกิดภาวะแคลเซียมเกาะเนื้อไต (nephrocalcinosis) โดยการศึกษาข้อมูลจากเวชระเบียนของทารกทุกคนที่มีอายุครรภ์น้อยกว่า 32 สัปดาห์ หรือมีน้ำหนักแรกเกิดต่ำกว่า 1250 กรัม ที่รอดชีวิตจนได้รับการตรวจไตด้วยคลื่นความถี่สูง แบ่งทารกเป็น 2 กลุ่ม คือกลุ่มที่มีและไม่มี nephrocalcinosis และเปรียบเทียบข้อมูลของทารกเกี่ยวกับประวัติครอบครัวเป็นนิ่วในไต อายุครรภ์ น้ำหนักแรกเกิด ความเจ็บป่วย ปริมาณสารน้ำที่ได้รับในช่วง 6 สัปดาห์แรกหลังคลอด ระยะเวลาที่ได้รับการช่วยหายใจ ยาที่ได้รับ ระดับแคลเซียม ฟอสเฟต และ alkaline phosphatase ในซีรั่ม ระยะเวลาที่ได้รับสารอาหารทางหลอดเลือด ระยะเวลาอยู่โรงพยาบาล และความผิดปกติของไต ผลการศึกษาพบว่าจากทารกจำนวนทั้งสิ้น 36 คน ทารกมี nephrocalcinosis 14 คน (38.9%) เมื่อเปรียบเทียบกับทารกที่ไม่มี nephrocalcinosis ปรากฏว่าปัจจัยที่เกี่ยวข้องกับภาวะ nephrocalcinosis ที่มีความสำคัญทางสถิติคือ ความรุนแรงของโรคทางเดินหายใจ การเกิดPDA ความต้องการการรักษาด้วยออกซิเจนเป็นเวลานาน การได้รับยาขับปัสสาวะ furosemide และการได้รับสารน้ำปริมาณจำกัด nephrocalcinosis หายไปในทารก1คนจากจำนวนทารก 7 คนที่ได้รับการตรวจไตซ้ำด้วยคลื่นความถี่สูงเมื่อเวลาประมาณ 2 เดือนหลังจากตรวจครั้งแรก พบมีการติดเชื้อทางเดินปัสสาวะเฉพาะในทารกที่มี nephrocalcinosis 3 คน (21.4%)

การศึกษานี้แสดงให้เห็นว่าอุบัติการณ์การเกิดภาวะแคลเซียมเกาะเนื้อไต(nephrocalcinosis) ในทารกเกิดก่อนกำหนด น้ำหนักน้อยมากมีค่อนข้างสูง ในการดูแลรักษาทารกเหล่านี้ควรป้องกันมิให้เกิดปัจจัยเสี่ยงดังกล่าวข้างต้น ทารกน้ำหนักน้อยเหล่านี้ควรได้รับการตรวจกรองโรค nephrocalcinosis เมื่ออายุครรภ์ครบกำหนดหรือก่อนให้ออกจากโรงพยาบาล