THE INCIDENCE OF NEPHROCALCINOSIS IN VERY LOW BIRTH WEIGHT NEONATES

S. M. Milani [1], N. Ataei* [2], E. Amini [3] and M. R. Azizi [2]

1) Department of Neonatology, The Children's Hospital Medical Center, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2) Department of Pediatric Nephrology, The Children's Hospital Medical Center, Faculty of Medicine , Tehran University of Medical Sciences, Tehran, Iran
3) Department of Neonatology, Imam Khomeini Hospital, Faculty of Medicine , Tehran University of Medical Sciences, Tehran, Iran

Abstract- The risk of nephrocalcinosis (NC) in preterm neonates is considerable, but conflicting numbers are given for the actual incidence (10-65%). Furosemide induced hypercalciuria is said to be the main risk factor. We assessed prospectively the incidence, causes and outcome of NC in very low birth weight (less than 1500 g) preterm neonates by serial renal ultrasound scans and urine analysis. Infants born elsewhere and transferred after 24 hours of age were excluded, as those who where discharged or died before 7 days of age. Two infants developed NC, giving an overall incidence of 4% in the study group. The follow-up showed persisting NC in both preterm neonates. Urinary investigations showed no consistent findings in infants with NC. In conclusion, the incidence of NC was lower in our population than is usually reported. Routine renal ultrasound scanning of very low birth weight preterm neonates is valuable in detecting NC.

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INTRODUCTION

Nephrocalcinosis (NC) refers to diffuse precipitation and growth of either calcium oxalate (CaOx) or calcium phosphate in the parenchyma of the kidney (1, 2). In 1982, Hufnagle *et al.* described NC in preterm neonates for the first time (3). In a recent study, postmortem examinations of 44 preterm and term infants showed deposition of typical CaOx in 18.5% and both calcium phosphate and CaOx in 4.5% (4).

Ultrasonography (US) has been found to be a sensitive and reliable method for the detection of NC (5-7). Cortical NC is defined as multiple, fine granular crystal deposition within the renal cortex leading to an increase in echogenicity. In contrast, medullary NC first looks like slight papillary crystal deposition which is later followed by an increase in such crystal deposition, visible in a change of corticomedullary differentiation in renal ultrasound (8).

The incidence of NC in preterm neonates varies widely from 10% to 65%, depending on different study populations, US criteria and US equipment and gestational age (4, 9-18).

In the first months of life, NC can develop as a result of an imbalance between stone-inhibiting and stone-promoting factors. Furosemide therapy, because of its hypercalciuric effects, is the most frequently mentioned provoking factor for the development of NC in preterm neonates (3, 10, 16). In infancy, medullary NC can develop as a result of renal tubular acidosis, hypervitaminosis D,

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*** Corresponding Author:**
N. Ataei, Department of Nephrology, Children's Hospital Medical Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 66930024
Fax: +98 21 66930024
E-mail: ataiinem@sina.tums.ac.ir

hyperparathyroidism and hyperoxaluria (19, 20). It has recently been observed that in association with a hyperprostaglanduric tubular syndrome hypercalciuria and hypokalemia are also present in preterm infants (21). Treatment with corticosteroids, xanthines (22, 23), and gentamicin (21) may also contribute to stone formation. Infants with a low birth weight and a short gestational age appear to run a higher risk of developing NC (10, 13, 16, 18, 22, 23). Besides, elevated urinary excretion of further lithogenic substances (*e.g.*, oxalate, uric acid) or the decreased excretion of inhibitory parameters (*e.g.*, citrate) under specific medication (*e.g.*, dexamethasone), parenteral nutrition, long term ventilation, high intake of calcium, phosphorus and ascorbic acid, high excretion ratio of urinary calcium/citrate and urinary calcium/creatinine contribute to the high incidence (18).

In view of conflicting reports of the incidence of NC in the face of known risk factors, this study was designed to determine the incidence and the possible contributory factors towards renal NC in our population of preterm neonates.

MATERIALS AND METHODS

From November 2001 to December 2002, all infants born before 37 completed weeks of gestation with a birth weight below 1500 g who were admitted to neonatal intensive care unit (NICU) of Valiasr Hospital within 24 hours of birth were included in the study. Infants born elsewhere and transferred after 24 hours of age were excluded, as those who were discharged or died before 7 days of age. We obtained informed consent from all parents.

Reports were searched for the following data: gestation age, birth weight, nutrition, medication, calcium phosphate supplementation, mechanical ventilation, acid-base status, (serial) renal ultrasound examination, urinary calcium excretion and other diagnoses.

After 7 days of age, all infants had ultrasound scans of the urinary tract with a real time sector scanner using a 7.5 MHz and 5 MHz probe. Parasagittal and coronal views of the kidneys were routinely taken and coronal views usually provided the best definition of the anatomy of the kidney.

In all infants, ultrasound scan was performed every 3 weeks until discharge or death. Infants with persistent NC were later seen for ultrasound and urine examinations at least every 3 months at our neonatal outpatient clinics.

RESULTS

Two out of the 50 infants developed NC giving as overall incidence of 4% in the study. Renal calcification was unilateral. In both cases NC was detected at the age of 14 days equally affecting both sexes. The mean duration of hospitalization was 8 days (range 7 to 60 days). There were six deaths in those without NC before discharge from hospital.

Both infants who developed calcification, were prescribed regular furosemide treatment, compared with 34 (70.1%) of the unaffected infants. The dose of furosemide that had been given to the two with NC was 5.1 mg/kg/day. The total doses in individual infants ranged from 122-216 mg. Both infants were on fluid regimens of less than 170 ml/kg/day, approximately for all the time that they were receiving furosemide. None had received chlorothiazide.

In the 40 infants who did not have NC, the total furosemide dose in individual infants ranged from 0-208 mg; only four received more than 100 mg/kg/day. All of these infants received more than 160 ml/kg/day of fluid. There was no difference between the infants with and without NC in the amount of vitamin D supplementation, the type of milk mixture they received, the incidence of osteopenia of prematurity, prolonged acidosis and hypercalcemia, or the administration of other drugs. Calcium excretion was routinely measured once weekly until discharge in all the preterm infants. Urinary calcium:creatinine ratio mg/mg ranged from 0.2-0.9 (normal < 0.6), and this did not correlate in any way with NC. Hypercalciuria was found in 5/50 preterm infants. Urinary calcium excretion was high (> 0.6), in infants with NC. Of two infants with NC, the mean duration of hospitalization was 16 days, the mean duration of total parenteral nutrition was 12 days, and the mean duration of ventilation was 13 days.

In 64%, acute respiratory syndrome developed, 26% had an infection, and 24% developed apnea bradycardia syndrome.

Bronchopulmonary dysplasia was not observed in any case. Microscopy of urine did not show hematuria or other abnormalities in any infant, and although osmolality and pH varied, there was no association between any measurement and nephrocalcinosis. In addition to two infants with NC, we did not find any structural abnormality in the urinary tract on ultrasound.

We did not observe complete remission of NC in affected infants 3 months after discharge. Both of the infants with NC at term showed NC at the age of 3 months.

DISCUSSION

The incidence of NC was lower in our population of preterm neonates compared to that in the literature (4, 10-14), which may reflect improvements in neonatal intensive care, in particular the antenatal use of steroids and surfactant and improved nutrition.

Ultrasound scanning has proved to be a useful and effective mean for diagnosing NC. The greater sensitivity of modern ultrasound equipments in diagnosing NC suggests that early reports may have underestimated the incidence of NC (10, 14, 24). Cramer et al. reported a sensitivity of 96% and specificity of 85% using ultrasound compared with computed tomography and postmortem histological diagnosis in a rabbit model (6). NC develops during the neonatal period when preterm infants are exposed to various risk factors (2, 6, 10, 13, 18, 25). The incidence of NC was rather low in our population of preterm infants compared to that in the recent literature (Table 1).

Prospective studies and improvements in diagnostic ultrasound have allowed earlier detection of NC in large numbers. Different diagnostic criteria are probably responsible for the even higher incidence reported by Jacinto *et al.* (10). One reason for the difference in the data given in the literature with incidence numbers ranging from 10% to 65% is the different approach and interindividual interpretation of ultrasound examinations.

Table 1. Incidence of nephrocalcinosis in preterm infant, in the last studies

References	Year of publication	Incidence
Jacinto *et al.* (9)	1988	65% (20/31)
Woolfield *et al.* (10)	1988	8.3% (3/36)
Short and Cooke (12)	1991	27% (21/79)
Sheu *et al.* (13)	1993	10% (5/50)
McCormick *et al.* (3)	1996	18% (8/44)
Campfield *et al.* (24)	1997	16% (17/104)
Present series	2005	4% (2/50)

Campfield *et al.* observed NC in 16% of preterm infants when using a 7.5 MHz transducer, but only in 6% when using a 5 MHz transducer (4). The extreme incidence (65%) in the study by the Jacinto *et al.* (10), might also be explained by such a difference in technique when compared with newer studies (7.5 vs. 5MHz transducer) (10, 13). We used both a 5 MHz and 7.5 MHz transducer for renal US. The lower incidence of NC in the recent studies could also be explained by improvements in the treatment of preterm infants: time of mechanical ventilation decreased, furosemide dosages were reduced and the duration of parenteral nutrition was shorter. For example, in the study of Short and Cooke, mean duration of mechanical ventilation was 41 days in infants with NC (13), but it was only 9 days in our patients.

All studies seem to confirm that smaller and more immature infants are more susceptible to calcification. Consistently, the mean gestation of our patients was higher than those reported by Ezzedeen *et al.* (17). In this study, both affected boy and girl were equally at risk, similar to other investigations (12).

Possible causes of increased medullary echogenicity in the preterm infants other than NC are renal candidiasis, cytomegalovirus infection, infantile polycystic kidney disease or renal vein thrombosis (19-21, 26). These causes were excluded in our patients' population. Urinary tract infections (UTI) might occur frequently in infants with NC (3, 9). In this study UTI did not occur in any of 2 infants with NC. Both of the infants with NC at term showed NC at the age of 3 months. This is inconsistent with the results of Saarela *et al.*, demonstrating that the ultrasonographic

abnormalities that develop in the first months of life disappear in the majority of patients within a period of months to years (16).

Furosemide therapy, because of its hypercalciuric effects, is most frequently mentioned provoking factor for the development of NC in preterm neonates (3-10, 16), but Schell-Feith *et al.* showed that furosemide is not the major cause of the early development of NC in preterm neonates (18). In our study, only 2 (4%) of 36 (72%) preterm infants receiving furosemide, had NC. Thirty six of 50 infants had received furosemide, so we can not have the furosemide prescription as a main risk factor in developing NC. We do not know the exact cause of NC, but both infants with NC had a longer time of hospitalization and total parenteral nutrition and we can claim that these factors have some effects on incidence of NC.

Calcium excretion was higher than normal range in both infants with NC and in the group without NC; there were only three cases with higher calcium excretion. In our study, both infants with NC had received dexamethasone and we may suggest this as a risk factor of nephrocalcinosis. One of 2 preterm infants with NC was under mechanical ventilation for a long time and we can assume this as a risk factor of NC.

In conclusion, US is a valuable modality in diagnosing NC in very low weight preterm neonates. We suggest that US should be included as a routine part of the evaluation of the preterm babies. It is necessary to perform more studies to realize the risk factors of developing of hypercalciuria and NC, and probably discovering the methods of prevention and treatment of NC in this group of neonates.

REFERENCES

1. Gilsanz V, Fernal W, Reid BS, Stanley P, Ramos A. Nephrolithiasis in premature infants. Radiology. 1985 Jan; 154(1):107-110.
2. Noe HN, Bryant JF, Roy S, Stapleton BF. Urolithiasis in preterm neonates associated with frusemide therapy. J Urol. 1984; 132: 93-94.
3. Hufnagle KG, Khan SN, Penn D, Cacciarelli A, Williams P. Renal calcifications: a complication of long-term furosemide therapy in preterm infants. Pediatrics. 1982 Sep; 70(3):360-363.
4. McCormick FC, Brady K, Keen CE. Oxalate nephrocalcinosis: a study in autopsied infants and neonates. Pediatr Pathol Lab Med. 1996 May-Jun; 16(3):479-488.
5. Alon U, Brewer WH, Chan JC. Nephrocalcinosis: detection by ultrasonography. Pediatrics. 1983 Jun; 71(6):970-973.
6. Cramer B, Husa L, Pushpanathan C. Nephrocalcinosis in rabbits--correlation of ultrasound, computed tomography, pathology and renal function. Pediatr Radiol. 1998 Jan; 28(1):9-13.
7. Dick PT, Shuckett BM, Tang B, Daneman A, Kooh SW. Observer reliability in grading nephrocalcinosis on ultrasound examinations in children. Pediatr Radiol. 1999 Jan; 29(1):68-72.
8. Patriquin H, Robitaille P. Renal calcium deposition in children: sonographic demonstration of the Anderson-Carr progression. AJR Am J Roentgenol. 1986 Jun; 146(6):1253-1256.
9. Downing GJ, Egelhoff JC, Daily DK, Alon U. Frusemide-related renal calcification in the premature infant. A longitudinal ultrasonographic study. Pediatr Radiol. 1991; 21: 563-565.
10. Jacinto JS, Modanlou HD, Crade M, Strauss AA, Bosu SK. Renal calcification incidence in very low birth weight infants. Pediatrics. 1988 Jan; 81(1):31-35.
11. Woolfield N, Haslam R, Le Quesne G, Chambers HM, Hogg R, Jureidini K. Ultrasound diagnosis of nephrocalcinosis in preterm infants. Arch Dis Child. 1988 Jan; 63(1):86-88.
12. Adams ND, Rowe JC. Nephrocalcinosis. Clin Perinatol. 1992 Mar; 19(1):179-195.
13. Short A, Cooke RW. The incidence of renal calcification in preterm infants. Arch Dis Child. 1991 Apr; 66(4 Spec No):412-417.
14. Sheu JN, Chen CH, Lue KH, Chen JY, Tsau YK, Chen JH. Renal calcification in very low birth weight infants. Am J Nephrol. 1993; 13(1):6-11.
15. Karlowicz MG, Katz ME, Adelman RD, Solhaug MJ. Nephrocalcinosis in very low birth weight neonates: family history of kidney stones and ethnicity as independent risk factors. J Pediatr. 1993 Apr; 122(4):635-638.

16. Saarela T, Vaarala A, Lanning P, Koivisto M. Incidence, ultrasonic patterns and resolution of nephrocalcinosis in very low birthweight infants. Acta Paediatr. 1999 Jun; 88(6):655-660.
17. Ezzedeen F, Adelman RD, Ahlfors CE. Renal calcification in preterm infants: pathophysiology and long-term sequelae. J Pediatr. 1988 Sep; 113(3):532-539.
18. Schell-Feith EA, Kist-van Holthe JE, van Zwieten PH, Zonderland HM, Holscher HC, Swinkels DW, Brand R, Berger HM, van der Heijden BJ. Preterm neonates with nephrocalcinosis: natural course and renal function. Pediatr Nephrol. 2003 Nov; 18(11):1102-1108.
19. Jequier S, Kaplan BS. Echogenic renal pyramids in children. J Clin Ultrasound. 1991 Feb; 19(2):85-92.
20. Chiara A, Chirico G, Comelli L, De Vecchi E, Rondini G. Increased renal echogenicity in the neonate. Early Hum Dev. 1990 Apr; 22(1):29-37.
21. Shultz PK, Strife JL, Strife CF, McDaniel JD. Hyperechoic renal medullary pyramids in infants and children. Radiology. 1991 Oct; 181(1):163-167.
22. Kamitsuka MD, Williams MA, Nyberg DA, Fox KA, Lee DL, Hickok D. Renal calcification: a complication of dexamethasone therapy in preterm infants with bronchopulmonary dysplasia. J Perinatol. 1995 Sep-Oct; 15(5):359-363.
23. Schell-Feith EA, Kist-van Holthe JE, Conneman N, van Zwieten PH, Holscher HC, Zonderland HM, Brand R, van der Heijden BJ. Etiology of nephrocalcinosis in preterm neonates: association of nutritional intake and urinary parameters. Kidney Int. 2000 Nov; 58(5):2102-2110.
24.Campfield TJ, Bradnarek FJ, Pappagallo M, Hampf F, Ziwacz J, Welmann J, Rochwell G, Bradan G, Flynn-valone G, Neylan M, Pangan A. Nephrocalcinosis in preterm infants: variability in ultrasound detection. J Perinatal. 1999; 19: 498-500.
25. Seyberth HW, Rascher W, Schweer H, Kuhl PG, Mehls O, Scharer K. Congenital hypokalemia with hypercalciuria in preterm infants: a hyperprostaglandinuric tubular syndrome different from Bartter syndrome. J Pediatr. 1985 Nov; 107(5):694-701.
26. Herman TE, Siegel MJ. Pyramidal hyperechogenicity in autosomal recessive polycystic kidney disease resembling medullary nephrocalcinosis. Pediatr Radiol. 1991; 21(4):270-271.