Renal Calcification Incidence in Very Low Birth Weight Infants

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ABSTRACT. Serial ultrasound examinations were performed on 31 neonates with birth weights of less than 1,500 g for the detection of renal calcifications. Renal calcifications occurred in 20 (64%) of the infants at a mean age of 39.3 ± 26.7 days of life. Infants with renal calcifications had shorter gestations (28.2 ± 1.8 v 31 ± 1.4 weeks, P < .004) and lighter birth weights (924 ± 195 v 1,338 ± 100 g, P < .004) than those infants without renal calcifications (n = 11). Furosemide administration was more common in the infants with renal calcifications (65% v 9.1%, P < .001). The mean total dose of furosemide administered before renal calcifications were noted was 9.59 ± 7.25 mg/kg. The 20 neonates with renal calcifications had a mean urine calcium level of 12.0 ± 6.8 mg/kg/24 hours, mean urine calcium to creatinine ratio of 1.32 ± 1.03 (range 0.3 to 4.45), and a mean alkaline phosphatase concentration of 961 ± 327 IU. Initial parathyroid hormone levels were not different between the two groups, and subsequent determinations in infants with renal calcifications did not differ significantly from initial values. Renal calcifications are fairly common among very low birth weight infants, particularly in those receiving supplemental calcium and furosemide therapy. Although long-term implications of such findings are not known, close monitoring of renal function by serial determinations of urine calcium and urine calcium to creatinine ratios may identify those infants at risk for renal calcifications. Pediatrics 1988;81:31-35; renal calcification, very low birth weight infant.

Modern perinatal care has resulted in reduced mortality for very low birth weight (≤1,500 g) infants.1,2 Although the survival rate has improved, these infants tend to have complicated hospital courses. Major problems during the first few weeks of life include respiratory difficulties related to pulmonary immaturity, symptomatic ductus arteriosus, and a high incidence of CNS hemorrhage. Among survivors, in a significant number chronic lung disease eventually may develop.

In the course of these infants' hospitalization and treatment, especially during the acute stage of illness, supplemental calcium and phosphate are given in an effort to prevent nutritional rickets. Furosemide, a potent diuretic, is often given to reduce pulmonary edema and thus improve pulmonary gas exchange.3 Furosemide and calcium supplements via total parenteral nutrition have diuretic effects and may impose an additional burden on an immature renal system.4-7 Prolonged use of such therapy has been reported to cause renal calcifications as a result of excessive calcium loss in the urine as calcium oxalate or calcium phosphate.8 This may lead to hematuria, infection, hydronephrosis, and renal failure.

Reported cases to date fail to substantiate the actual incidence of such problems, specifically the degree of biochemical abnormalities related to the occurrence of renal calcifications. Thus, this study was designed to establish the incidence of renal calcifications in very low birth weight infants and to determine the contributing factors that increase the risk for the development of renal calcifications.

MATERIALS AND METHODS

All very low birth weight infants admitted to our neonatal intensive care unit were eligible for the study. Infants without ultrasound evaluation, with incomplete biochemical and laboratory studies, or by parental request were excluded from the study. Informed written parental consent was obtained prior to each infant's enrollment. The study protocol was approved by our institutional review board.
Pertinent clinical data recorded were the diagnosis; gestational age; birth weight; intrauterine growth classification; indications, amount, and duration of diuretic therapy; and the amount and duration of calcium supplementation. Exogenous calcium intake was calculated on a milligram per day basis and furosemide as milligrams per kilogram.

Serial urinalysis, serum calcium, phosphate, alkaline phosphatase, and creatinine values were obtained during the third week of life and repeated every 3 weeks until hospital discharge. Urine collection was done for determination of urine calcium, phosphate, and creatinine concentrations during a 12-hour period at 3 weeks and thereafter every 3 weeks. Urine calcium to creatinine ratio was calculated. Parathyroid hormone levels were determined at the time the initial samples were obtained and repeated whenever renal calcifications were detected or prior to discontinuation of diuretic therapy. All laboratory analyses were done in duplicate in our clinical laboratory. Parathyroid hormone (C-terminal, midmolecule) levels were done, in duplicate, by using the radioimmunoassay method. The normal range is 50 to 330 pg/mL with interassay and intraassay coefficient of variation of 9.7% and 7.1%, respectively.

Real-time ultrasound examinations of the kidneys using a 7.5-MHz transducer were performed during the third week of life and repeated every 3 weeks until discharge. These were repeated more often if clinically indicated. Ultrasound evaluations were done by an experienced ultrasonographer (M.C.), who was unaware of which patients required calcium supplementation or diuretic therapy.

Statistical comparisons were performed using $x^2$, Student’s $t$ test, and Wilcoxon rank sum test, where appropriate. Data are expressed as means ± 1 SD, unless otherwise indicated.

### RESULTS

From October 1985 to September 1986, 39 very low birth weight infants were enrolled in the study, and 31 completed the study. Six were withdrawn by parental request, and two infants died prior to the initial ultrasound evaluation. Renal calcifications developed in 20 (64%) infants (RC group), noted at a mean age of 39 ± 26.7 days, and did not develop in 11 (36%) infants (NRC group). Nine infants had unilateral and 11 had bilateral foci of calcifications.

Infants in whom renal calcifications developed were smaller and more immature compared with the NRC group (Table 1). Furosemide was administered to 13 (65%) of the infants in the RC group and to one (9.1%) infant of the NRC group ($P < .001$). In seven very low birth weight infants who did not receive furosemide renal calcifications developed. Their mean birth weight and gestational age were 1,042 ± 227 g and 29.3 ± 1.1 weeks, respectively. When compared with infants without renal calcifications, they were of lower birth weight ($P < .01$) and lower gestational age ($P < .05$). Mean total dose of furosemide administered before detection of renal calcifications was 9.25 ± 7.25 mg/kg. A higher percentage of these infants had respiratory distress syndrome and bronchopulmonary dysplasia, although the difference was not statistically significant (Table 1).

Initial serum calcium and phosphate concentrations during the third week of life were within physiologic ranges in both the RC and the NRC group. The mean alkaline phosphatase was 961 ± 327 IU in all infants and did not differ between the infants with or without renal calcification. Initial parathyroid hormone levels were not different between the RC and NRC group. Subsequent determinations in the RC group did not differ significantly from the initial values.

Urine samples from both groups were relatively

### TABLE 1. Infants With and Without Renal Calcifications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Renal Calcification Group</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants With (n = 20)</td>
<td>Infants Without (n = 11)</td>
</tr>
<tr>
<td>Birth wt (mean g ± SD)</td>
<td>924 ± 195</td>
<td>1,338 ± 100</td>
</tr>
<tr>
<td>Gestational age (mean wk ± SD)</td>
<td>28.2 ± 1.8</td>
<td>31 ± 1.4</td>
</tr>
<tr>
<td>No. (%) receiving furosemide</td>
<td>13 (65)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>No. (%) with respiratory distress syndrome</td>
<td>16 (80)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>No. (%) with bronchopulmonary dysplasia</td>
<td>4 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (mean mL/24 h ± SD)</td>
<td>86 ± 30.8</td>
<td>83.2 ± 36.4</td>
</tr>
<tr>
<td>Calcium (mean mg/kg/24 h ± SD)</td>
<td>12.0 ± 6.8</td>
<td>7.6 ± 9.7</td>
</tr>
<tr>
<td>Calcium to creatinine ratio (mean ± SD)</td>
<td>1.32 ± 1.03</td>
<td>0.75 ± 0.76</td>
</tr>
</tbody>
</table>

* There were 48 urine samples from the infants with and 14 samples from the infants without renal calcifications.
Table 2. Furosemide Effect on Infants With Renal Calcifications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Infants Receiving Furosemide</th>
<th>Infants Not Receiving Furosemide</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth wt (mean g ± SD)</td>
<td>869 ± 160</td>
<td>1,042 ± 227</td>
<td>.07</td>
</tr>
<tr>
<td>Gestational age (mean wk ± SD)</td>
<td>27.9 ± 1.8</td>
<td>29 ± 1.1</td>
<td>.08</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (mean mL/24 h ± SD)</td>
<td>73.6 ± 32.6</td>
<td>66.4 ± 18.8</td>
<td>.30</td>
</tr>
<tr>
<td>Calcium (mean mg/kg/24 h ± SD)</td>
<td>13.6 ± 6.0</td>
<td>9.6 ± 7.1</td>
<td>.15</td>
</tr>
<tr>
<td>Calcium to creatinine ratio (mean ± SD)</td>
<td>1.80 ± 1.00</td>
<td>0.98 ± 0.72</td>
<td>.08</td>
</tr>
</tbody>
</table>

Fig 1. Ultrasound of kidneys in patient born at 28 weeks’ gestation with birth weight of 870 g obtained at 24 weeks’ chronologic age. Echogenic focus (arrow) in lower pole of left kidney is apparent.

Fig 2. On repeat examination 3 weeks later, previously identified calcification in the lower pole of left kidney (arrow) was still present.

alkaline, with pH values ranging from 6.0 to 7.0. Urinalysis in one patient in the RC group showed 10 to 20 WBCs per high-power field; repeat urinalysis yielded the same result. In this patient, catheter-obtained urine for culture was positive for >100,000 colonies per milliliter of Providencia stuartii for which the patient was treated for seven days with IV ampicillin. Urinalysis and cultures were negative after completion of antibiotic therapy. Ultrasound at the time of infection showed no significant change from the one obtained 3 weeks previously. This showed bilateral renal calcifications and minimal distention of the left renal pelvis.

Comparison for urine volume, urine calcium, and calcium to creatinine ratio between the NRC and the RC groups showed a trend for the RC group to have higher urine volume, urinary calcium excretion, and calcium to creatinine ratio, although the differences were not statistically significant (Table 1).

Among patients with renal calcification, as noted in Table 2, urine volume, urine calcium, and calcium to creatinine ratio were all elevated in the group of subjects receiving furosemide compared with those who did not receive the drug, but the differences were not statistically significant. Data for one patient who did not receive furosemide were excluded because of incompleteness of urine collection.

During the first 2 weeks of life, calcium supplements ranged from 200 to 400 mg/kg/d in both RC and NRC groups. The patients who were smaller and were unable to tolerate enteral feedings received calcium and phosphate supplementation for more time. The differences in urine phosphate excretion in both groups were not statistically significant at any time.

A representative case of ultrasound findings of the kidneys in one patient are shown in Figs 1 and 2. Ultrasound done at 24 weeks of life (Fig 1) showed an echogenic focus seen in the lower pole of the left kidney. On repeat examination 3 weeks later (Fig 2), the previously identified calcification in the lower pole of the left kidney was again visualized. These findings did not disappear until discharge. We did not perform systematic contrast radiographic studies to confirm our ultrasound findings.

Discussion

Hufnagle et al² reported four cases of renal calcification complicating long-term furosemide therapy in very low birth weight infants. Goldsmith et
al\(^4\) attempted to study the effect of calcium gluconate supplementation on urinary calcium excretion and showed that the calciuria appeared to increase progressively with continued calcium gluconate therapy, placing the sick newborns at risk for development of renal calcification.

Furosemide, an anthranilic derivative, has been investigated by several workers and its potency as a diuretic has been well documented.\(^5\) It exerts its diuretic action primarily by inhibiting sodium reabsorption from the ascending loop of Henle and the proximal tubule.\(^6\) Calcium reabsorption is inhibited at the ascending loop of Henle and whether or not it affects reabsorption at the proximal tubular site is unknown. This diuretic agent has been used on a chronic basis for various conditions such as hypertension in infants and neonates,\(^10\) bronchopulmonary dysplasia,\(^7\) renal insufficiency of various causes,\(^14\) and respiratory distress syndrome.\(^8\) A recent study by Warshaw et al\(^12\) using growing rats to monitor the effect of furosemide administration showed a significant increase in calcium excretion in the treated group. Urinary calcium loss increased by twofold compared with that of the controls during the first 24 hours of collection. With prolonged therapy, calcium loss in the urine increases threefold.\(^12\) This calciuric effect does not diminish with time; if this phenomenon occurred in premature infants, the effect may be deleterious. Furthermore, parathyroid hormone secretion may be increased which might theoretically mobilize calcium out of bone to maintain normal serum calcium concentrations. Venkataraman et al\(^13\) examined four infants receiving long-term furosemide therapy who were hypercalciuric; apparent hyperparathyroidism and demineralization developed in three of these infants. They suggested that, in these infants, furosemide induces hypercalciuria which results in secondary hyperparathyroidism, a finding similar to that noted in adult patients.\(^14\) Hyperparathyroidism did not develop in our patients with renal calcifications.

Ong et al\(^15\) studied acute and chronic calciuric effects on adult mongrel dogs after experimentally inducing hypercalcemia in these animals. They showed decreasing urinary calcium loss with increasing length of furosemide administration and also a decreased response to dehydrotachysterol when administered concomitantly with furosemide. A similar result was documented by Lindy and Tarssarien\(^16\) in human adults with congestive heart failure. These findings are somewhat different from a study by Warshaw et al\(^12\) using growing rats. Physiologic responses to the exogenous calcium and diuretics in very low birth weight infants may be different from adult dogs or humans.

Nordin\(^17\) suggested the usefulness of creatinine output as a physiologic "constant" against which calcium might be measured. Creatinine serves as a standard reference related to lean body mass and skeletal mass. The range given is 0.03 to 0.28 in normal subjects.\(^17\)

Hypercalciuria has been defined as urinary calcium excretion exceeding 4 mg/kg per 24 hours.\(^18\) The calcium to creatinine ratio is no more useful than the measurement of the 24-hour calcium output if expressed in milligrams per kilogram per 24 hours, but it is less dependent upon the accuracy of urine collection.\(^17\) Thus, if 4 mg/kg per 24 hours is the upper limit of increased urinary calcium excretion and 0.3 is the upper limit of the calcium to creatinine ratio, then these infants have values significantly greater than the normal limits shown in Table 1. It is then expected that these infants are predisposed for the development of renal calcifications.

Nineteen of 20 very low birth weight infants in our study in whom renal calcifications developed who were followed by serial ultrasound examinations did not exhibit any significant abnormalities with regard to BP or renal function.

In summary, renal calcifications are common among very low birth weight infants as detected by real-time ultrasound. The smaller, sicker, and more immature infant appears to have increased risk for renal calcification development. Use of a potent diuretic, such as furosemide, and exogenous calcium supplementation in these infants with resulting increased urinary calcium excretion may be additional risk factors. However, in small, sick infants renal calcifications may develop even without the use of diuretics. In premature infants in whom calcium balance is unstable, this phenomenon may prove deleterious.

Although long-term implications of such findings are not known, close monitoring by serial ultrasound and renal function by urine calcium and creatinine excretion may prove informative for all infants at increased risk for renal calcifications. Long-term follow-up of these patients is not available to date and would warrant further study.

ACKNOWLEDGMENT

This work was supported by Clinical Research grant 543-85 from the Children's and Memorial Foundation, Long Beach, CA.

REFERENCES


CONFIDENCE INTERVALS RATHER THAN P VALUES

The excessive use of hypothesis testing at the expense of more informative approaches to data interpretation is an unsatisfactory way of assessing and presenting statistical findings from medical studies. We prefer the use of confidence intervals, which present the results directly on the scale of data measurement.

Submitted by Student

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*Pediatrics* 1988;81;31

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