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Furosemide-related renal calcifications in the premature infant

A longitudinal ultrasonographic study

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Abstract. Low birthweight infants treated with chronic furosemide therapy are at risk for the development of intrarenal calcifications. A prospective longitudinal renal ultrasound investigation was conducted to study the correlation of diuretic therapy, clinical course and ultrasonographic findings. Of 117 premature infants studied ultrasonographically upon discharge from the hospital, 20 had intrarenal calcifications. Eight patients at age 16.3 ± 2.6 months had sonographic resolution of renal calcifications, 6.6 ± 1.1 months after furosemide therapy had been discontinued. Of the 12 patients with persistent calcifications, 4 died from severe pulmonary disease and autopsy in 3 of them confirmed the ultrasonographic diagnosis. All 12 children but 2 continued to receive furosemide for their chronic lung disease demonstrating significant association between chronic use of loop diuretics and persistance fo the renal calcifications ($p < 0.001$). Two patients required nephrolithotomy and 4 suffered from recurrent urinary tract infections. In 4 patients, 5 kidneys were of small size and in 2 bilateral collecting system dilation was noted. We conclude that discontinuation of furosemide therapy is associated with resolution of the renal calcifications. On the other hand, continued treatment with furosemide is associated with high renal morbidity which indicates ongoing clinical and ultrasonographic follow-up.

Furosemide therapy in premature infants has been associated with hypercalciuria and intrarenal calcifications; e. g. nephrocalcinosis and nephrolithiasis [1–3]. Previously, renal calcifications were identified by plain radiographs; however, the application of ultrasound techniques has offered an improved diagnostic capability [4, 5].

Several anecdotal reports have described the resolution of furosemide-related intrarenal calcifications in this population; however, the overall long term natural history of this iatrogenic problem has not yet been defined [6, 7]. We undertook a prospective longitudinal study to investigate the correlation between the use of furosemide, clinical course and serial ultrasonographic findings of low birthweight infants with furosemide-related intrarenal calcifications.

Materials and methods

Infants with birthweights less than 1750 grams, respiratory distress syndrome and chronic lung disease treated with furosemide underwent ultrasound imaging of the urinary tract prior to hospital discharge. Those infants with evidence of renal calcifications were then evaluated by sonographic imaging at 3 to 6 month intervals.

Sonographic examination of the urinary system included sagittal and transverse images of kidney and bladder. Imaging was performed with an Ultramark 8 or 9 real time sector scanner (Advanced Technology Laboratories, Inc., Bothell, WA) with either a 5 or 7.5 mHz transducer. Kidney measurements were obtained using criteria of Dinkel [8]. Intrarenal calcification in this study was defined as medullary nephrocalcinosis or nephrolithiasis.

Nephrolithiasis was determined by abnormal echogenic foci, with or without acoustical shadowing in the calyces or papillary portion of renal pyramids or renal pelvis. Diffusely increased echoge-

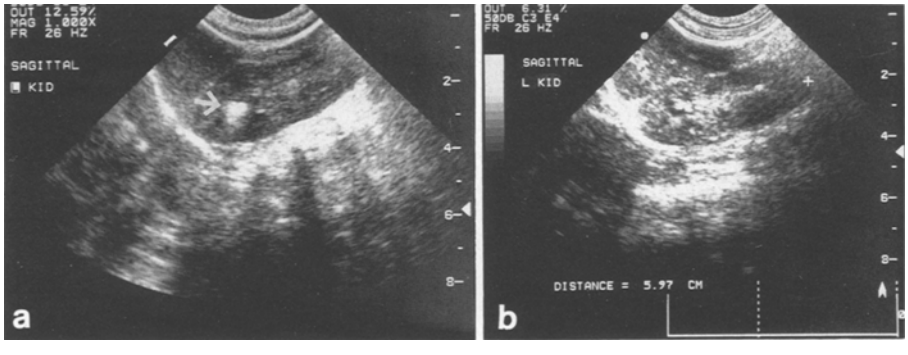

Fig. 1. **a** Renal ultrasound of a 26 week gestation infant showing diffuse intrarenal calcifications *(arrow)*.
b A repeat ultrasound performed 7 months later demonstrating resolution of the intrarenal calcification

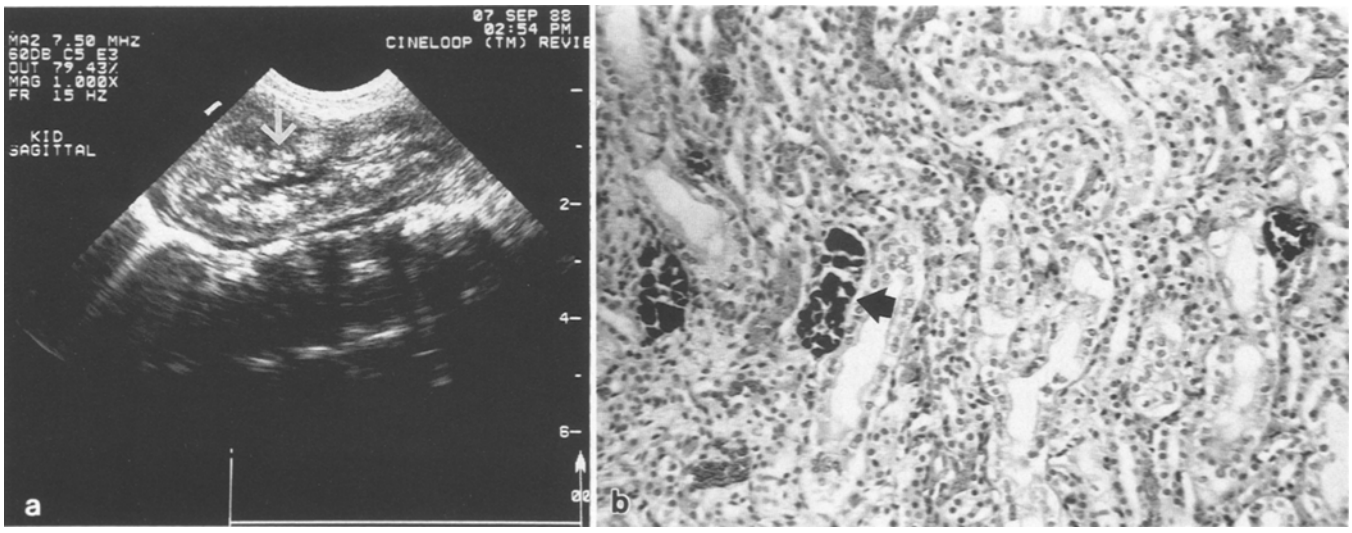

Fig. 2. **a** Renal ultrasound of a premature infant treated with furosemide for severe chronic lung disease demonstrating nephrocalcinosis *(arrow)*. **b** Autopsy specimen of this patient demonstrating intratubular calcifications *(arrow)* consistent with medullary nephrocalcinosis

nicity in the renal medullary pyramids was interpreted as nephrocalcinosis.

Renal ultrasound images were reviewed by a pediatric radiologist (J.C.E.) blinded to the history and clinical course. Data are expressed as mean values ± SEM. Statistical analysis was done with the Chi-square test with Yate's correction for small groups. Significance was determined at the level of $p < 0.05$.

Results

During a 30 month study period, 117 patients met entry criteria and had renal ultrasound imaging prior to their hospital discharge. The presence of intrarenal calcification was identified in 20 patients (17%), of them 12 were males. Calcifications were found bilaterally in 15 infants. Two infants required nephrolithotomy for ureteral obstruction. Four patients were treated for repeated urinary tract infections.

During the long term follow-up period, calcifications resolved in 8 patients, in all of whom furosemide therapy had been discontinued (Fig. 1). Ultrasonographic resolution of the calcifications in these infants occurred 6.6 ± 1.1 months (range 3–17 months) after furosemide therapy had been discontinued and at a mean chronological age of 16.3 ± 2.6 months (range 7–28 months).

Four patients with persistent intrarenal calcifications died from severe cardiorespiratory complications of bronchopulmonary dysplasia at a mean age of 13.1 ± 1.4 months. All 4 continued to be maintained on furosemide until the time of their death. Autopsy examinations of the kidneys in 3 of these patients demonstrated histologic evidence of nephrocalcinosis and nephrolithiasis (Fig. 2).

The remaining 8 patients with persistent calcifications were between 8 and 30 months of age (14.6 ± 1.8 months) and all continued to be on furosemide except for 2 who had furosemide discontinued 4–5 weeks prior to the last ultrasonographic examination. Analysis of the association between treatment with furosemide and renal calcifications revealed that infants maintained on the diuretic therapy were more likely to have persistent calcifications than those in whom diuretic therapy had been discontinued ($p < 0.001$). Related ultrasound pathology included 5 instances of decreased kidney length observed in 4 patients and bilaterally dilated ureters in 2 additional patients.

Discussion

Nephrocalcinosis and nephrolithiasis in premature infants who receive furosemide therapy are thought to result from the calciuric effect of the drug which acts on the ascending limb of the loop of Henle. Diminished sodium reabsorption in this segment is linked with decreased calcium reabsorption and increased calcium excretion. This process is thought to result in the formation of medullary calcifications and nephrolithiasis. The most effective diagnostic tool for the detection of intrarenal calcifications is ultrasound [5]. Indeed, the findings on three autopsies confirmed the ultrasonographic findings.

Progression of medullary nephrocalcinosis to formation of kidney stone on one hand and conversely resolution of the nephrocalcinosis after discontinuing furosemide in other cases can be explained by the autopsy finding of the renal calcifications within the tubular lumen (Fig. 1). Because of the high rate of regeneration of the renal tubule cells, once the drug is discontinued the calcifications are probably being eliminated with restoration of normal ultrasonographic patterns. However, in other patients with continuous formation of intratubular calcifications they may propogate into the collecting system and serve as a nidus for stone formation. Why some patients develop stones and others do not is yet unclear. The finding of calcium deposits in medullary tubules and concommitant calyceal stone formation are consistent with the Anderson-Carr-Randall progression theory of calculus formation [9].

The reversibility of nephrocalcinosis acquired at a younger age has been documented anecdotally also by

others in children with furosemide-related nephrocalcinosis [6, 7] and Bartter's syndrome [10]. However, no longitudinal data on the correlation between ultrasonographic findings and diuretic therapy have been reported.

Our data relates a significant correlation between discontinuation of furosemide therapy with the resolution of intrarenal calcifications. Of 12 patients greater than 1 year of age, all eight in whom furosemide therapy has been discontinued had total resolution of the calcifications. Our data indicate that the radiologist and the clinician can expect resolution of the renal calcifications within 18 months after discontinuing the diuretic.

Those patients who must be continued on furosemide should continue to be followed for related renal morbidity. As described in this study, repeated urinary tract infections, diminished kidney growth, urinary tract obstruction and the potential need for surgical intervention indicate the need for serial renal ultrasound studies.

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