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ORIGINAL ARTICLE

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Nephrocalcinosis in preterm infants: a single center experience

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Abstract The risk of nephrocalcinosis in preterm infants 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 examined retrospectively the incidence, causes and outcome of nephrocalcinosis in preterm infants born in our hospital from 1988 to 1998 (*n*=2190). An abnormal renal echogenicity or nephrocalcinosis was seen in 31 infants (29.7±3.3 weeks gestational age; 1307±690 g birth weight). Nephrocalcinosis was diagnosed in 16, hyperechoic kidneys (HK) in 10 and Tamm-Horsfall kidneys in 5 infants. Main risk factors were low gestation age and birth weight, length of hospitalization, variations in acid-base status, length of assistant ventilation and hypercalciuria at diagnosis. The incidence of nephrocalcinosis was 0.73% [1.7% for low birth weight infants (VLBW)]. Taking the cases of nephrocalcinosis and HK together, incidence was calculated to be 1.2% overall and 2.5% for VLBW infants, but increased to 7% in 1998. The follow-up showed persisting nephrocalcinosis or hyperechoic kidneys in 8/26 preterm infants. In conclusion, the incidence of nephrocalcinosis was lower in our population than is usually reported. The numbers have, however, increased over the past few years. From the follow-up it was obvious that long-term observation of preterm infants is necessary and that complications might arise in the long run.

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Introduction

The risk of nephrocalcinosis in preterm infants is controversial [1–6]. The numbers given for the incidence vary between 10% and 65% (Table 1), with the highest incidence in high risk preterm infants (<1000 g birth weight, <30 weeks gestational age [1–6]). Nephrocalcinosis is mostly due to either parenchymal calcium oxalate (CaOx) or calcium phosphate deposition [7, 8]. This was recently shown in postmortem examinations with typical CaOx in 18.2% and calcium phosphate deposits in 4.5% of preterm and term born infants examined [4].

Furosemide induced hypercalciuria is considered to be the main risk factor for the development of nephrocalcinosis in preterm infants [1, 3, 7, 9, 10]. The list of risk factors should also include 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 or long-term ventilation [1, 11–17].

Studies on long-term follow-up, morbidity and complications are scarce [11, 18, 19]. It is, however, beyond debate that nephrocalcinosis could lead to complications if persistent. We therefore examined incidence, causes and outcome of abnormal renal echogenicity and nephrocalcinosis in our population of preterm infants.

Table 1 Incidence of nephrocalcinosis in preterm infants

References	Year of publication	Incidence
Jacinto et al.	1988	65% (20/31)
Short and Cooke	1991	27% (21/79)
Sheu et al.	1993	10% (5/50)
McCormick et al.	1996	18% (8/44)
Campfield et al.	1997	16% (17/104)
Pfitzer et al.	1998	10% (3/30)

Materials and methods

We analyzed all available reports of preterm infants born in our hospital between 1988 and 1998. We therefore used data stored using the diagnostic code for Pediatrics at the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE) of the University of Cologne [20]. We then included those preterm infants in the study who fitted one of the given criteria:

1. Born <37 weeks gestation age *and*
2. The diagnosis of:
   - Hyperechoic kidneys (group A)
   - Tamm-Horsfall kidneys (group B)
   - or nephrocalcinosis (group C)

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.

The preterm infants were included in specific groups according to the ultrasonographic criteria:

Hyperechoic kidneys: diffuse increase in echogenicity of both kidneys, which is still visible after the 1st week of life, but will later resolve in follow-up ultrasound examinations. In preterm infants, such an increase in echogenicity is often found in combination with enlarged kidneys.

Tamm-Horsfall kidneys: a circumscript increase in echogenicity (cf. Fig. 1) near to the medullary pyramids during the first days of life, also combined with a large kidney volume. Tamm-Horsfall kidneys mostly disappear after 10–14 days (Fig. 2). The physiological loss of fluid during the first days of life, and in addition, the crystallization of mucoproteins are the culprit, for a reversible tubulus obstruction. As THP has a specific tendency to gel out rapidly, such an obstruction could lead to binding of Tamm-Horsfall protein (THP) with CaOx, Ca-phosphate, or urate crystals. Whether THP is a modulator of kidney stone formation or nephrocalcinosis is, however, a matter of debate [21, 22].

Nephrocalcinosis: Cortical nephrocalcinosis is defined as multiple, fine-granular crystal deposition within the renal cortex leading to an increase in echogenicity. In contrast, medullary nephrocalcinosis 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 (Fig. 3). Medullary nephrocalcinosis is now divided into different stages of severity [23]. However, such differentiation was not always done during the study period and is therefore not included in our evaluation.

Renal ultrasound is routinely performed in addition to head and/or hip ultrasound examinations. In infants with abnormal renal echogenicity ultrasound was performed every 2nd week until remission or discharge. Infants with persistent nephrocalcinosis or hyperechoic kidneys were later seen for ultrasound and urine examinations at least every 3–6 months at our Pediatric Nephrology outpatient clinics. For statistical analysis the Kruskal-Wallis and the Mann-Whitney test were performed using SPSS Software (SPSS, Chicago, IL).

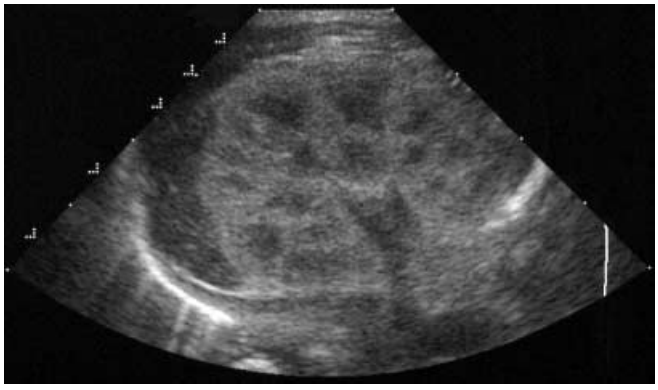

Fig. 1 Normal renal ultrasound of a preterm infant born 33 weeks gestational age; kidney parenchyme is still hyperechoic in comparison to adjacent liver and spleen

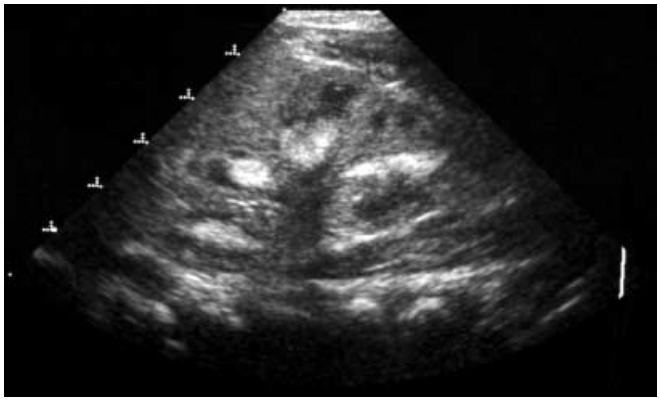

Fig. 2 "Tamm-Horsfall" kidney in a preterm infant during the first days of life with a reversible increase in echogenicity near to the medullary pyramids

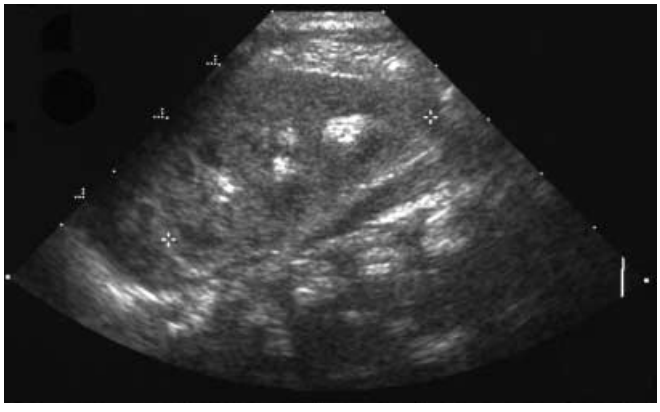

Fig. 3 Nephrocalcinosis in a preterm infant

Results

Out of 2190 preterm infants born between 1988 and 1998, only 31 preterm infants fulfilled the inclusion criteria. Of these, 16 preterm infants were diagnosed with nephrocalcinosis, 10 infants had persistent hyperechoic kidneys, and Tamm-Horsfall kidneys were found in 5 preterm infants (Fig. 4). Nephrocalcinosis developed either early or very late (4th vs 128th, mean 72nd, day of life).

The overall incidence of cases with abnormal renal echogenicity was only 1.42%, and that of nephrocalcinosis 0.73%. Incidence was higher in preterm infants with a birth weight below 1500 g, being 1.2% for nephrocalcinosis and 2.5% when cases with persistent hyperechoic kidneys were added. Both cases with nephrocalcinosis and persistent hyperechoic kidneys increased over the past few years, leading to an incidence of 3% for all pre-

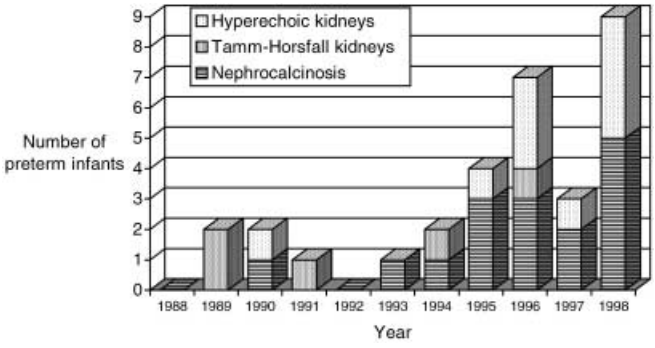

Fig. 4 Number of preterm infants with suspicious ultrasound findings between 1988 and 1998

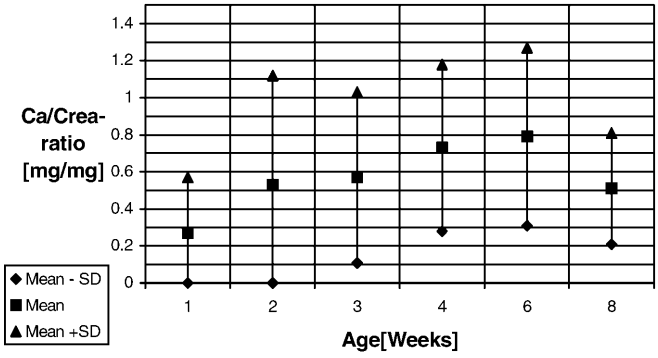

Fig. 5 Calcium excretion during the first 8 weeks of life

Table 2 Clinical data of preterm infants included in the study

	Group A (n=10) Hyperechoic kidneys	Group B (n=5) Tamm-Horsfall kidneys	Group C (n=16) Nephrocalcinosis
Gestation age (weeks)	30.7±3.2	32.4±2.3	28.3±3.0**
Birth weight (g)	1604±827	1615±523	1044±523
Duration of hospitalization (days)	54.5±30.5	46.6±24.8	139.8±180.6*
Furosemide dosage (mg/kg)	3.6±6.6	1.9±1.3	4.7±5.9
Dexamethasone dosage (mg/kg)	0.86±1.32	1.59±2.91	1.77±1.83
Methylxanthine dosage (mg/kg)	85.4±147.8	135.4±265.4	215.4±241.5
Calcium phosphate dosage (mg/kg)	28.5±33.9	24.3±54.3	57.4±52.2
Duration of mechanical ventilation (days)	3.0±3.9	8.0±5.7	14.9±14.5*
Acid base status: ΔpH >0.1	3.2±5.6	7.4±6.4	18.5±16.6*
Parenteral nutrition (days)	2.5±4.2	3.8±3.6	1.4±2.2

*P<0.05 C vs A/B, **P<0.05 C vs B

term infants in 1998 and 7% for such infants with a birth weight below 1500 g.

When comparing the clinical parameters for all three groups given in Table 2, preterm infants with nephrocalcinosis showed a lower gestation age, a longer duration of hospitalization and a longer requirement for mechanical ventilation (P<0.05). Medication and its dosage did not differ significantly between groups, with furosemide not necessarily given in patients with nephrocalcinosis. Preterm infants with nephrocalcinosis remained longer on and received a higher dosage of calcium phosphate supplementation (Table 2).

Ten out of the 31 preterm infants had a 1-min Apgar of <1. In 84%, acute respiratory distress syndrome developed, 68% had an infection, 45% developed apnea-bradycardia syndrome and bronchopulmonary dysplasia was found in 29%.

Relevant changes in acid base status with pH levels out of the physiological range were seen in 21/31 preterm infants, but were significantly longer and expressed more strongly in infants with nephrocalcinosis (ΔpH 0.27, pH_{min} 7.19) compared to those with Tamm-Horsfall kidneys (ΔpH 0.23, pH_{min} 7.23) or with hyperechoic kidneys (ΔpH 0.16, pH_{Min} 7.3).

Calcium excretion, which is routinely measured once weekly until discharge in all preterm infants, increased over the 1st weeks of life with a maximum at weeks 4–6 (Fig. 5). Hypercalciuria was found in 13/31 preterm infants (Ca/creatinine >0.7 mg/mg), but calcium excretion normalized during the first 2 months of life in ten infants. Hypercalciuria was diagnosed in 12 of the preterm infants with either nephrocalcinosis or hyperechoic kidneys, but in only one infant with Tamm-Horsfall kidneys. Mean calcium excretion was higher in preterm infants receiving furosemide and dexamethasone, and cumulative dosage of the latter was correlated with the mean calcium excretion (r=0.5). Furosemide dosage ranged from 0.5 to 1 mg/kg body weight in those infants receiving the medication.

A higher calcium excretion was observed at weeks 7 and 8 for preterm infants compared to those without methylxanthine medication (0.58±0.29 vs 0.22± 0.06 mg/mg, P<0.05). Methylxanthine dosage (theophylline in 2 and coffein-citrate in 12 infants) ranged from 5 to 10 mg/kg body weight, but reached 20 mg/kg in one preterm infant. Calcium excretion was also higher in preterm infants under total parenteral nutrition (TPN), being significantly higher in the 2nd week of life than the excretion of infants with oral nutrition (P<0.05). Duration of hypercalciuria was correlated with that of mechanical ventilation and the duration and height of changes in the acid base status (r=0.61 and 0.69, P<0.05).

Severe hypercalcemia was not observed in all groups, the mean blood calcium level being 2.31±0.39 mmol/l.

Blood phosphorus levels were 6.59±1.18 mg/dl and the vitamin D supplementation during hospitalization was 400 IU/kg body weight per day. Full parenteral nutrition included 2 g amino acids/kg body weight, 0.5 mmol calcium/kg and 1 mmol phosphorus/kg body weight per day.

Follow-up

All infants with nephrocalcinosis and persistent hyperechogenicity of the kidneys are followed by our Pediatric Nephrology outpatient clinics. Complete remission of nephrocalcinosis was observed in 5/16 preterm infants 6–12 months after discharge. After a follow-up of 3–6 years, only partial remission was seen in 3/16 infants, and nephrocalcinosis persisted in 4/16 infants. Four preterm infants with nephrocalcinosis were lost to follow-up. In half of the infants with hyperechoic kidneys, renal ultrasound normalized within 6 months. Kidneys, however, remained hyperechoic in 4/10 infants after 4–6 years, with one preterm infant lost to follow-up. We did not observe recurrent urolithiasis in our group of preterm infants, nor did we see an increased incidence of urinary tract infection in the preterm infants with abnormal renal echogenicity. During the follow-up, glomerular filtration rate remained normal for age related values. The urine concentration capacity expressed as urine osmolality and/or specific weight remained adequate in all ex-preterm infants followed. Acidosis did not develop.

Comparing the group with complete remission of nephrocalcinosis with the infants with persistent findings, preterm infants with remission received significantly lower dosages of furosemide, dexamethasone and methylxanthines ($P<0.05$). Total parenteral nutrition was longer in the group with persistent findings, as were the duration of mechanical ventilation and the changes in acid base status. Calcium excretion did, however, not differ between groups. In two of the infants with persistent nephrocalcinosis, hyperoxaluria and hypocitraturia were diagnosed, and in another infant and his twin brother isolated hyperoxaluria was found and treated.

Discussion

The incidence of nephrocalcinosis and hyperechoic kidneys was rather low in our population of preterm infants compared to that in the recent literature [1–6]. The number of such diagnosis did, however, increase over time up to a level of 7% in 1998 for preterm infants with a birth weight below 1500 g. This increase is best explained by the more regular use of routine ultrasound examinations over the past few years, which lead us to conclude that the numbers found in 1998 are more likely to express the exact incidence of nephrocalcinosis and persistent hyperechoic kidneys in our population.

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 the interindividual interpretation of ultrasound examinations. Campfield et al. observed nephrocalcinosis in 16% of preterm infants when using a 7.5-MHz transducer, but only in 6% when using a 5-MHz transducer [24]. The extreme incidence (65%) in the study by Jacinto et al. might also be explained by such a difference in technique, when compared to newer studies (7.5- vs 5-MHz transducer [3, 25, 26]). We used both a 5-MHz and a 7-MHz transducer for renal ultrasonographies.

The lower incidence of nephrocalcinosis in the latest 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 by Short and Cooke, mean duration of mechanical ventilation was 41 days in infants with nephrocalcinosis, but it was only 14.9 days in our patients [16].

Which findings might help explain why nephrocalcinosis developed? Preterm infants with nephrocalcinosis were younger, smaller and hospitalized significantly longer (Table 2). More often they had anemia (56%) and an apnea-bradycardia syndrome (56%). Length of ventilation was longer, changes in pH levels were more severe and the number of bronchopulmonary dysplasias higher. In addition, cumulative dosage of furosemide, dexamethasone and methylxanthines was higher, as was calcium phosphate supplementation. Parenteral nutrition was necessary for a longer period. The most obvious differences were found with regard to the necessity of mechanical ventilation and the severity of changes in acid base status, which were best explained by the more severe prematurity of infants with nephrocalcinosis [27, 28]. Abnormal renal echogenicity due to fungal infections was taken into consideration, but without any evidence of such infection we excluded it as the reason for the abnormal ultrasound.

Calcium excretion was elevated in only half of the preterm infants. In addition, furosemide induced hypercalciuria seems not to be the main risk factor, as furosemide was not given in a third of the preterm infants with nephrocalcinosis in our study and in none in the study of Sheu et al. [26]. As previously reported, calcium excretion was increased under dexamethasone and methylxanthine medication, as well as under total parenteral nutrition [11, 12, 29–31]. It would have been interesting to analyze the urinary excretion of other parameters influencing urinary saturation such as oxalate, uric acid and citrate [17, 32, 33]. Such measurements were, however, only started in 1998 and preliminary data allow us to suggest that hypocitraturia is one of the most important risk factors for the development of nephrocalcinosis in preterm infants [32, 33]. Both duration of mechanical ventilation and changes in acid base status not only influence calcium excretion, but can also be the culprits for such decreased citrate excretion.

Preterm infants with nephrocalcinosis were reported to be smaller and to have a lower gestational age than infants without that complication [3, 16, 26]. In our study,

the incidence of nephrocalcinosis was higher in the group of infants with a birth weight below 1500 g. Immaturity of the kidneys, especially in preterm infants born <34 weeks gestational age, should therefore be considered to be a risk factor [27, 28, 32].

Long-term prognosis varied in our patient population. In most of the infants, a complete or partial remission was observed. In 26% of preterm infants nephrocalcinosis and hyperechoic kidneys, however, persisted, which was comparable to the numbers given in previous publications, with persisting nephrocalcinosis in 44% and 45%, respectively [1, 9]. Therefore, a high morbidity and long-term complications might be expected in these infants. Saarela et al. found signs of renal tubular dysfunction in early childhood of ex-preterm infants and Jones et al. showed in a 7- to 8-year follow-up that ex-preterm infants with persistent hypercalciuria had a lower bone mineral density than term infants without hypercalciuria [18, 19]. Hence, further prospective studies are necessary to better explain the background of nephrocalcinosis in preterm infants, which might be a route to a (prophylactic) treatment.

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