ORIGINAL ARTICLE

Neonatal nephrocalcinosis: long term follow up

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Aims: To assess the spontaneous resolution of neonatal nephrocalcinosis and its long term effects on renal function.

Methods: Fourteen very low birthweight preterm babies with nephrocalcinosis were followed up at 5–7 years of age; 14 controls were matched for sex, gestation, and birth weight. Height, weight, blood pressure, and renal symptomatology were recorded, and a renal ultrasound scan was performed. Early morning urine osmolality and creatinine ratios of albumin, phosphate, calcium, oxalate and β microglobulin were determined. Urea and electrolytes in the study group were determined, and glomerular filtration rate (GFR) and TmP/GFR (tubular reabsorption of phosphate per GFR) were calculated. Statistical analysis was performed on a group basis using the Mann-Whitney confidence interval.

Results: Mean age was 6.9 years (range 5.81–7.68). An early morning urine osmolality >700 mOsm/kg was achieved in all cases. In two cases and four controls, the calcium/creatinine ratio was >0.7 mmol/mmol. In all cases, the GFR was normal (median 132.6 ml/min/1.73 m² (range 104.1–173.1)). Median TmP/GFR was 1.22 mmol/l (0.73–1.61), with two having levels below the normal range. These did not have persisting nephrocalcinosis. Nephrocalcinosis was found in three of the 12 cases scanned and one control. There were no significant differences in urine biochemistry.

Conclusions: Resolution of nephrocalcinosis occurred in 75% of cases. No evidence was found to suggest that nephrocalcinosis is associated with renal dysfunction in the long term. There was evidence of hypercalciuria in the cases and controls, suggesting that prematurity may be a risk factor.

Preterm babies are at risk of nephrocalcinosis, first described by Hufnagle *et al* in 1982.¹ The incidence has been found to be 16–64% in very low birthweight babies, and risk factors include low gestational age, low birth weight, frusemide use, aminoglycoside use, male sex, length of assisted ventilation, and length of hospital stay.^{2–6}

Although nephrocalcinosis is thought to predispose to urinary tract infection, renal colic, and haematuria, the long term consequences in preterm babies are unclear, and several studies have suggested a resolution of nephrocalcinosis in 20–60%.^{6–12} Some reports suggest that nephrocalcinosis may predispose to glomerular and tubular dysfunction,^{7,8} and others propose that prematurity alone leads to renal dysfunction, independent of nephrocalcinosis.¹⁰

In a previous study, we determined the incidence and aetiological factors associated with nephrocalcinosis in preterm babies either <1.5 kg at birth or gestation <32 weeks.² The aim of the present study was to follow up preterm babies found to have nephrocalcinosis and compare them with matched controls from the original study to determine whether nephrocalcinosis is associated with long term renal functional sequelae.

METHODS

In the original study, 16 out of 101 preterm babies had nephrocalcinosis (16%). On follow up of these 16 babies, one had died of a cause unrelated to renal dysfunction and one was not contactable, leaving a cohort of 14. Fourteen controls from the original study who did not have nephrocalcinosis were matched for birth weight (± 200 g), gestational age (± 1 week), and sex. Where more than one control in the pool met the criteria to match a case, one of the available controls was selected randomly. If the selected control refused to take part, another of the appropriate controls was selected at random from all those remaining. Both the nephrocalcinosis cohort and controls were re-evaluated at

5–7 years of age, using a local research ethics committee approved protocol.

Each child and parent was interviewed, and written informed consent obtained. The interview included specific questions on whether there had been a history of urinary tract infection or other urinary tract symptoms. The hospital case records of cases and controls were examined, and contact was made with the relevant general practitioner. Height, weight, and blood pressure were measured and compared with normal values.^{13,14} An early morning urine sample was collected before the child had anything to drink and sent for determination of osmolality, calcium, albumin, protein, phosphate, oxalate, $\beta 2$ microglobulin, and creatinine. If early morning urine osmolality was found to be <700 mOsm/l, intranasal desmopressin was administered and a follow up was performed four hours later. The patient group also had blood taken for determination of plasma urea and electrolytes, calcium, and phosphate. From this, glomerular filtration rate (GFR) in ml/min/1.73 m² was calculated using the formula

$$\text{GFR} = (49 \times \text{height (cm)}) / \text{plasma creatinine}^{15}$$

The renal tubular reabsorption of phosphate per GFR (TmP/GFR) was calculated using the formula

$$\text{TmP/GFR} = \text{PPO}_4 - (\text{UpPcr/Ucr}),$$

where PPO_4 = plasma phosphate (mmol/l), Up = urinary phosphate ($\mu\text{mol/l}$), Pcr = serum creatinine (mmol/l), and Ucr = urinary creatinine (mmol/l).¹⁶

Control patients did not have blood taken for ethical reasons.

A renal ultrasound was performed on cases and controls to determine renal length, morphology, and presence of nephrocalcinosis using an ATL 15000 Phillips Medical Systems scanner. Renal length was compared with normal values.¹⁷ All scans were carried out or checked by a single consultant radiologist, who was unaware of the neonatal renal ultrasound result. Four children defaulted from ultrasound leaving 24 (12 cases and 12 controls).

Table 1 Basic characteristics of the patients and controls in the study

	Controls	Patients
Gestational age (weeks)	28.5 (25–31)	27.5 (25–31)
Birth weight (g)	1210 (670–1870)	1180 (565–1880)
Age at follow up (years)	7.21 (6.38–7.68)	6.69 (5.81–7.09)

Values are median (range).

Statistical analysis was performed using a two tailed Mann-Whitney U test, with significance level 5%, and associated 95% confidence interval.

RESULTS

Median age at follow up for cases was 6.69 years and for controls 7.21 years. There was no significant difference in gestational age or birth weight between the groups (table 1). One patient and one control had height and weight <0.4th centile, with a further two patients and one control having heights and weights in the 2–9th centiles.

Only one patient had had confirmed urinary tract infection in the past, at age 1 month. Urinary tract imaging in the form of technetium-99m dimercaptosuccinic acid and micturating cystourethrogram were normal. One control had a history of frank haematuria and was found to have hypercalciuria and has subsequently been invited for follow up. In another case, mild hydronephrosis was noted on the neonatal scan, which had settled by 4 years of age. Three patients and one control had systolic hypertension, and one patient had systolic and diastolic hypertension. Blood pressure measurement was not possible in one control because of lack of cooperation.

Biochemistry

There were no significant differences in any of the urinary biochemical variables between the two groups (table 2).

One child had received frusemide for treatment of a heart condition. He had stopped medication three weeks before the study. He had no biochemical abnormalities of serum or urine.

All patients had normal GFR with a median of 132.6 ml/min/1.73 m² (104.1–173.1), and the median TmP/GFR was 1.22 mmol/l (0.73–1.61). Two patients had a TmP/GFR below the normal for age (0.73, 0.95). These were the only two patients who also had raised β_2 microglobulin/creatinine ratios (0.118, 0.139 mg/mmol). They did not have persisting nephrocalcinosis.

Six children (four controls and two cases) had evidence of hypercalciuria (Ca/Cr ratio >0.7 mmol/mmol). This persisted on repeat spot urine testing in four and was confirmed in three by 24 hour urine collection (normal <0.1 mmol/kg/day). One child has repeatedly failed to attend follow up appointments for 24 hour collection (table 3).

Of the three children (two cases and one control) with hypercalciuria confirmed by 24 hour urine analysis, all had

Table 3 Evidence of hypercalciuria

	Ca/Cr ratio 1 (mmol/mmol)	Ca/Cr Ratio 2 (mmol/mmol)	24 hour Ca collection (mmol/kg/day)
Case 1	0.96	1.95	0.19
Case 2	0.85	0.71	0.11
Control 1	0.75	0.57	0.06
Control 2	0.79	0.25	0.02
Control 3	1.47	0.79	0.18
Control 4	0.89	0.85	–

raised phosphate/creatinine ratios on spot testing. The one case also had raised β_2 microglobulin/creatinine ratio and a low TmP/GFR. There were no other biochemical abnormalities.

On questioning, there was no family history of renal disease, including renal stones, in any of the children.

Renal ultrasound

Two cases defaulted from renal ultrasound scan appointments, and as a result 12 cases and 12 controls were scanned.

Three of the 12 cases scanned (25%) and one control had evidence of nephrocalcinosis. This was bilateral except in one of the cases, and in this child nephrocalcinosis had been bilateral in the neonatal period. Of these children, only the control with nephrocalcinosis at follow up (6.2 years) had evidence of hypercalciuria. This child had normal renal ultrasound scans as a neonate and at 3 months of age and had no history of urinary tract infection, but had a recent episode of haematuria and remains under investigation.

Renal length was found to be reduced in four of 48 kidneys. One case and one control had one kidney <5th centile for height, and one case had bilateral small kidneys. These children had no other evidence of renal dysfunction.

DISCUSSION

We found that nephrocalcinosis resolved in 75% of patients scanned at a median age of 6.75 years. Downing *et al*⁷ found resolution in six of 10 (60%) preterm babies followed up at 1–2 years of age, and Ezzedeen *et al*⁸ found resolution in 44% (four of nine), and improvement in 56% (five of nine) very low birthweight preterm babies at 21.3 months of age. In their follow up study, Jones *et al*¹⁰ found that five out of 11 children (54%) had resolution at 4–5 years. Our finding of a higher rate of resolution is possibly due to the longer duration of follow up in our study. This conclusion is supported by the findings of Saarela *et al*¹¹ and Hoppe *et al*.¹² Hoppe *et al* in a retrospective study identified 16 preterm babies with nephrocalcinosis, which had resolved on ultrasound in 31% by 12 months and in 75% between 3 and 6 years. Saarela *et al* studied a group of babies with neonatal nephrocalcinosis classified on renal ultrasound findings into peripheral, scattered, and extensive. Each child had annual scans until resolution or to the age of 5–6 years. All of those

Table 2 Urinary biochemistry

Variable	Controls	Patients	95% CI	p Value
Ca/Cr (mmol/mmol)	0.35 (0.06–1.47)	0.56 (0.07–0.96)	–0.36 to 0.18	0.50
Osmolality (mOsm/kg)	938 (743–1214)	947 (749–1061)	–122 to 94	0.75
Phosphate/Cr (mmol/mmol)	4.45 (2.30–6.70)	4.05 (1.40–7.30)	–1.00 to 1.40	0.87
Albumin/Cr (mg/mmol)	1.0 (0.4–3.8)	0.8 (0.5–2.0)	–0.6 to 0.5	0.98
Protein/Cr (mmol/mmol)	0.008 (0.006–0.019)	0.008 (0.005–0.020)	–5.18 to 0.01	0.99
Oxalate/Cr (mmol/mmol)	0.05 (0.03–0.09)	0.051 (0.005–0.10)	–0.020 to 0.020	0.90

Values are median (range). Differences assessed by the Mann-Whitney U test. CI, Confidence interval.

with peripheral nephrocalcinosis had complete resolution by 1 year of age, the seven with scattered changes by 3–4 years. Of those with extensive changes, one baby died, and two of the remaining three had persisting nephrocalcinosis at 5–6 years, indicating a higher rate of resolution with time, with more extensive changes taking longer to disappear. We did not undertake such an ultrasound classification of nephrocalcinosis at the time of the original study, but we feel it is likely that those with persisting nephrocalcinosis will show resolution later in life, although longer term follow up will be required.

Our study indicated there was no evidence of impaired renal function or urine concentrating capacity as indicated by normal GFR and early morning osmolalities. Only two out of 14 children had reduced TmP/GFR, which, in association with raised β_2 microglobulin/creatinine ratio, is probably a subtle indication of proximal tubular dysfunction. One of these children also had hypercalciuria, although in both nephrocalcinosis had resolved. As controls did not have these tests performed, it is not possible to conclude whether neonatal nephrocalcinosis was causal. Other urinary biochemical variables were not different between the two groups. These results differ from those of Downing *et al.*,⁷ who followed 27 children to 14.1 months of age and found that those who had nephrocalcinosis ($n = 10$) had a higher urinary calcium/creatinine ratio and a lower tubular reabsorption of phosphate and tubular acidification capacity than those who did not have nephrocalcinosis ($n = 17$). Ezzedeen *et al.*⁸ suggested that there may be a reduction in GFR in children who had neonatal nephrocalcinosis when they were evaluated at a mean of 21.3 months. However, this was a small study of only nine patients, with no controls. Compared with our study, these studies were performed on children at a significantly younger age when renal function is not yet fully developed. Jones *et al.*¹⁰ followed up their cohort of 11 babies at a later age of 4–5 years, and the results showed no significant glomerular or tubular dysfunction associated with neonatal nephrocalcinosis in keeping with our own findings. This also concurs with Hoppe *et al.*,¹² who found that GFR and urinary osmolality in children with neonatal nephrocalcinosis were normal for age related values at follow up.

Six children in the study had evidence of hypercalciuria. Urinary Ca/Cr ratio was used, as this required only spot fasting samples from the children and has been shown to be useful as a screening tool in the diagnosis of hypercalciuria.¹⁸ Three of the five children who have supplied 24 hour urine samples were found to have raised calcium excretion. Numbers are too small to draw any conclusions, but neonatal nephrocalcinosis does not appear to be a risk factor. This again is in keeping with the findings of Jones *et al.*,¹⁰ who reported abnormal calcium load tests in three cases and five controls at 4–5 years of age, indicating that hypercalciuria appeared to be a consequence of prematurity independent of neonatal nephrocalcinosis. Hoppe *et al.*¹² noted increased calcium excretion in 13 of 31 preterm babies in the first 8 weeks of life, but did not comment on hypercalciuria at follow up. In a further study of 46 preterm children and 40 term matched controls aged 7–8 years, Jones *et al.*¹⁹ found that hypercalciuria was significantly more likely in the preterm group and was associated with raised serum aminoglycoside concentrations in the neonatal period. Aminoglycoside antibiotic use is well recognised as a cause of tubular dysfunction in the newborn period,²⁰ but whether this is long lasting is not known. We have reviewed data from our original study on neonatal nephrocalcinosis and ascertained that, of the three subjects with confirmed hypercalciuria at follow up, two had toxic gentamicin concentrations in the neonatal period, and the other had had exposure to

What is already known on this topic

- Preterm babies are at risk of developing nephrocalcinosis
- Hypercalciuria occurs in some premature children

What this study adds

- Nephrocalcinosis resolves in most cases by 7–8 years of age and does not cause significant renal impairment
- Prematurity not nephrocalcinosis appears to be a risk factor for hypercalciuria

gentamicin, with no toxic concentrations identified. All were of 27 weeks gestation and birth weight less than 1000 g.

Hypercalciuria is related to renal tubular abnormalities, abnormal handling of salt, increased prostaglandin E2 production, and abnormal synthesis of 1,25-dihydroxy vitamin D3. It is associated with renal morbidity in childhood—for example, haematuria, frequency dysuria syndrome, and renal calculi^{21–22}—and it has been shown to adversely affect bone mineral density and height at 7–8 years of age.^{19–23} In view of this potential morbidity and the ease of performing spot urine samples in babies, calcium/creatinine ratios, for which normative preterm values have been proposed,²⁴ may be a useful screening tool for distinguishing those babies at risk of hypercalciuria.

We did not measure urinary citrate, a powerful inhibitor of renal stone formation. This was measured in our original study, and no significant correlation with nephrocalcinosis was found.²⁵

Only one patient with neonatal nephrocalcinosis had experienced urine infection or haematuria. Four patients and one control had high blood pressure on one reading taken on the day of the hospital visit. This clearly may be related to anxiety and will be kept under review.

SUMMARY

Nephrocalcinosis persisted in 25% of patients at a median of 6.7 years, but we found no evidence to suggest that it is associated with renal dysfunction or symptoms in the long term, but further studies on those with persistent nephrocalcinosis are necessary. Although preterm babies may be at higher risk of developing hypercalciuria, nephrocalcinosis does not appear to be a risk factor, and we would not recommend undertaking routine renal ultrasound scans on very low birthweight preterm babies for nephrocalcinosis, as this appears to be benign. However, a case could be made for screening for hypercalciuria on discharge by doing a spot urinary calcium/creatinine ratio, particularly on those who have had exposure to toxic concentrations of aminoglycosides.

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