Neonatal Nephrocalcinosis and Diagnostic Implications

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Abstract

Nephrocalcinosis and its outcome has been widely studied in the preterm population. There is a paucity of data regarding nephrocalcinosis in term babies. Prospective case series, in which ten neonates were included in the study from November 2013 and April 2014. All neonates with nephrocalcinosis diagnosed by ultrasound of kidney, ureters, bladder (KUB) done antenatally or during evaluation for urinary tract infection in neonates with hyperbilirubinemia/sepsis were included. All preterm neonates and neonates with congenital urinary tract anamolies were excluded from this case series. Cases were followed to know the outcome of the condition by follow-up ultrasonography. Follow-up ultrasound kidneys after 2-4 weeks revealed no evidence of nephrocalcinosis in majority of the cases. In one case, hypocitrateuria was documented. Hence, nephrocalcinosis is a transient phenomenon but needs close monitoring with follow-up scans.

In this case series we investigated nephrocalcinosis with early follow-up and ultrasound of kidneys to compare the baseline findings.This helped us in defining absolute outcome to the parents in case of neonatal nephrocalcinosis. Moreover, it helped our fellows in making timely diagnosis and proper counselling.

Keywords: Nephrocalcinosis, neonate, ultrasound.

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Introduction

Renal calcifications are common in very low birth weight infants and full-term neonates who have had a difficult neonatal course. The two types of calcification associated with the urinary tract are urolithiasis and nephrocalcinosis (NC). Urolithiasis is macroscopic calcification in the urinary collecting system, while nephrocalcinosis is a microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidney[1]. The reported incidence of NC is 17-64% in pre-terms[2]. The reason for this common occurrence is multifactorial. Exposure of immature kidneys to nephrotoxic drugs, furosemide, corticosteroids and xanthenes are important factors in pre-term infants[3]. In term neonates and in older children the imbalance between crystal inhibitors (citrate and magnesium) and crystal promoters (calcium, uric acid, oxalate) plays a major role in the pathogenesis of renal calcifications[4]. The disorders associated with such imbalance include: primary hyperparathyroidism, subcutaneous fat necrosis, idiopathic hypercalciuria, distal renal tubular acidosis, Barter's syndrome and primary hyperoxaluria and hypocitraturia, Dent disease and Lowe syndrome[5].

Nephrocalcinosis, and even nephrolithiasis, usually clinically silent, are picked up on screening ultrasonography on high-risk population or in patients' presenting with haematuria or urinary tract infection (UTI). Although very rarely, renal failure could be the initial presenting feature as well[5,6]. NC can be detected by conventional radiography, ultra-

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sonography (US) or computer tomography (CT). High-resolution US is the best method for detecting and monitoring nephrocalcinosis. Low-dose CT may be necessary to detect urolithiasis, but only in late childhood[7]. Myracle et al.[8] recommend criteria for ultrasonographic diagnosis of nephrocalcinosis that require hyperechoic foci in the renal pyramids or calyces either producing shadowing or seeming to be at least 3 mm in diameter demonstrable in different planes.

The morbidity and mortality associated with neonatal nephrocalcinosis depends on the underlying aetiology. Fortunately, renal calcifications resolve in 75-85% of neonatal intensive care unit (NICU) patients in the first postnatal year[6].

Pharmacologic treatments according to the aetiological factors include, proper hydration, thiazide diuretics (e.g. hydrochlorothiazide), and magnesium or citrate supplementation. It has been observed that most stones are less than 5 mm in diameter and pass spontaneously and therefore do not require specific therapy. Surgical intervention is rarely indicated[9].

In Pakistan, there is paucity of data on this subject, even though clinical observations are frequent. Therefore, there is a vaccum in Pakistani literature, thus, the need for to publish case series.

Case series

Prospectively, all neonates with nephrocalcinosis admitted in NICU were included. All patients were admitted in the first week of life in Liaquat National Hospital between November 2013 and April 2014. Oral and written informed consent was taken and the ethics committee of the hospital approved the study protocol. Non-probability consecutive sampling technique was used.

Ten neonates were included in this case series. It is a rare finding in neonates hence the small sample size. The basis of being included in the study was nephrocalcinosis found over ultrasound of kidney, ureters, bladder (KUB) done antenatally or during evaluation for urinary tract infection in neonates with hyperbilirubinemia/sepsis. All preterm neonates and neonates with congenital urinary tract anomalies were excluded from the study.

Workup for nephrocalcinosis, including arterial blood gas analysis, serum calcium, urinary calcium/creatinine ratio, urinary magnesium, citrate and oxalate was performed.

Ultrasonography of the kidneys was used to detect NC. Senior consultant radiologist performed the US examinations using state of the art equipment with a 7 to 7.5 MHz small-part transducer (Toshiba, Zoetermeer,). Transverse and longitudinal images were made of both kidneys. The radiologists were not informed about the treatment and medication of the patients. US was performed at admission and at 2 weeks after 1st ultrasound. Nephrocalcinosis was defined as the presence of brightreflections in the medulla or cortex that was reproducible both in transverse and longitudinal directions with or without acoustic shadowing. The reflections varied from small flecks of 1 to 2 mm, white dots larger than 2 mm, to completely echodense pyramids[4].

A total of 10 neonates with neonatal nephrocalcinosis were included. All neonates were full-term without any apparent risk factors. Seven of the ten neonates presented with urinary tract symptomatology. One presented with antenatal scan showing nephrocalcinosis and two with deranged renal functions. A number of neonates had urinary tract infection while screening for focus of infection in neonates with sepsis who initially presented with hyperbilirubenemia. These neonates were then screened by ultrasonography for any urinary tract abnormality. US kidneys done for these complaints revealed hyperechoic foci suggestive of nephrocalcinosis.

Workup for nephrocalcinosis showedone case which had persistent findings on ultrasound imaging, the aetiology was found to be hypocitrateuria. On follow-up at one year, the child was thriving well with ultrasonography findings suggestive of resolution phase.In rest of the cases no aetiology could

be determined. Follow-up ultrasound kidneys after 4 weeks surprisingly revealed no evidence of nephrocalcinosis in rest of the cases.

The mean age of presentation of was found to be 3.5 days. There was no significant difference with regards to gender as the study revealed male to female ratio to be 1:1. Table 1, shows a brief summary of all the cases enrolled in the study and reason for US in the cases has been summarised in Table 2. Resolution of nephrocalcinosisin terms of outcome was seen in 70% (complete resolution of nephrocalcinosis), 10% (persistence of nephrocalcinosis) and 20% were lost to follow up.

Discussion

Neonatal nephrocalcinosis is a condition in which calcium level in the kidneys of neonates is increased. The two types of calcification associated with the urinary tract are urolithiasis and nephrocalcinosis. Urolithiasis is macroscopic calcification in the urinary collecting system while nephrocalcinosis is a microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidney[1]. Urolithiasis, not a frequent finding in NC is also suggested by a large prospective study, where none of the patients with NC developed urolithiasis during a 2-year follow-up period[10].

The morbidity and mortality associated with nephrocalcinosis depends on the underlying associated disease with the type rather than on the nephrocalcinosis itself.

NC is a known entity in pre-term babies due to variety of factors[4]. Although literature review has shown multiple cases of NC in full term babies, but there seems to be no report of idiopathic nephrocalcinosis in term babies.

Although CT scan is the most sensitive modality for detecting nephrocalcinosis but a study comparing ultrasound and CT in the diagnosis of nephrocalcinosis demonstrated a sensitivity of 85-91% with ultrasound, 86-92% with CT, and only 66-82% with plain kidney, ureters, bladder radiograph[11]. Myracle et al.[8] recommend criteria for ultrasonographic diagnosis of nephrocalcinosis that require hyperechoic foci in the renal pyramids or calyces either producing shadowing or seeming to be at least 3 mm in diameter demonstrable in different planes.

But it must be remembered that not all cases of medullary hyperechoic foci in NICU patients represent renal calcification. The differential diagnosis includes transient acute renal injury, pyelonephritis, granuloma secondary to CMV or candidiasis, fibrosis and urate deposits[6].

Once NC is detected on ultrasound, a panel of tests including serum electrolytes, creatinine, calcium, arterial blood gas analysis, urinary calcium to creatinine ratio, 24-hour urinary calcium excretion and urine analysis is conducted. Further testing includes urinary oxalate, citrate, uric acid and magnesium levels, parathyroid hormone and thyroid-stimulating hormone levels, CT scan may also be used to determine the cause of NC.

It is helpful to separate the causes of renal calcification in NICU patients into three groups: (i) normocalcemichypercalciuric, (ii) hypercalcemic-hypercalciuric, and (iii) normocalcemic-normocalciuric. Very low birth weight (VLBW) infants often have multifactorial causes (e.g. acute renal injury, chronic furosemide, corticosteroids) for nephrocalcinosis[6].

A study from Glasgow revealed resolution of nephrocalcinosis in 75% of cases with no evidence of renal dysfunction in long-term follow-up[12]. In our study, we also observed that nephrocalcinosis is a transient phenomenon with complete resolution in most of the cases. Another study, "Nephrocalcinosis in preterm infants: a single center experience", was conducted in University Children's Hospital Germany published in 2002, which showed persisting nephrocalcinosis or hyperechoic kidneys in 8/26 preterm infants, rest of them showed transient entity[10].

We had 10 cases of term neonates that were initially reported as nephrocalcinosis but follow-up ultrasound after 2 weeks showed complete resolu-

Table 1. Summary of all neonates with nephrocalcinosis admitted in the neonatal intensive care unit of a tertiary care hospital of Karachi

S.No	Age (days)	Gender	Reason for ultrasonography	Ultrasound findings	Underlying aetiology	Outcome
1	2	Male	Deranged renal functions	Nephrocalcinosis	Undetermined	Resolution
2	3	Female	Evaluation of UTI	Nephrocalcinosis	Undetermined	Resolution
3	5	Female	Evaluation of UTI	Nephrocalcinosis	Hypocitrateuria	Persistence of nephrocalcinosis
4	4	Male	Evaluation of UTI	Nephrocalcinosis	Undetermined	Resolution
5	5	Female	Deranged renal functions	Nephrocalcinosis	Undetermined	Resolution
6	5	Female	Evaluation of UTI	Nephrocalcinosis	Undetermined	Resolution
7	2	Male	Evaluation of UTI	Nephrocalcinosis	Undetermined	Loss to follow up
8	1	Male	Antennal scan showing nephrocalcinosis	Nephrocalcinosis	Undetermined	Resolution
9	7	Female	Evaluation of UTI	Nephrocalcinosis	Undetermined	Resolution
10	2	Male	Evaluation of UTI	Nephrocalcinosis	Undetermined	Loss to follow up

Table 2. Reason for ultrasonography in neonates admitted in the neonatal intensive care unit of a tertiary care hospital of Karachi

	Frequency	Percent
Evaluation of UTI	7	70.0
Deranged renal functions	2	20.0
Antennal scan showing nephrocalcinosis	1	10.0
Total	10	100.0

tion in all except one case; hence no extensive workup was performed in the remaining cases. This raised the suspicion whether these neonates had nephrocalcinosis at all in first place or it was simply medullary hyper-echogenicity that mimicked nephrocalcinosis. This needs further studies.

This brings to light the importance of correctly diagnosing NC in full-term babies. The predisposing risk factors should be identified and co-related with the ultrasonography findings. Repeat imaging is advised in idiopathic cases before an extensive workup is taken up. Although CT scan is also a good modality, it is not recommended because of hazard of radiation exposure. Definitive criteria should be ensured before labelling any neonate with renal calcifications because the diagnosisnot only needs extensive workup but also has significant impact on parental psychology.

The rationale of our study is to investigate the condition and early follow up with US KUB after 2 weeks to compare the baseline findings. This will help us in defining absolute outcome to the parents in case of neonatal nephrocalcinosis. Moreover, it will help our fellows in making timely diagnosis and proper counselling.

Our point of discussion was to diagnose the transient or persistent variety in selected cases and to determine the certain outcome in neonates with nephrocalcinosis before having any final counselling session with the family. The results of our study with the selected series of 10 neonates and above mentioned studies suggest that neonatal nephrocalcinosis can be a transient phenomenon with complete resolution later in life and is not always associated with morbidity and mortality, so a physician should be clear about the aetiology and outcome before making any final verdict.

Conclusion

Neonatal nephrocalcinosis is a transient phenomenon and needs close follow-up as our results showed transient type in 75% neonates.The results

are comparable with another study discussed earlier.

Conflict of interest

Authors have no conflict of interests and no grant/funding from any organisation for this study.

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