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# EARLY SIGNS, LASTING EFFECTS: A LOOK AT CLINICAL MANIFESTATIONS AND TREATMENT OUTCOMES IN CHILDREN WITH HYPERCALCIURIA AND NEPHROCALCINOSIS

**[1]Eriona Lika, [2]Aldiona Rama and [3]Bledar Hoxha**

[1]Pediatrics Department, Emergency Unit, University Hospital Center "Mother Theresa"
[2]Pediatrics Department, Nephrology Unit, University of Medicine, Tirana, Albania
[3]Public Health Department, University of Medicine, Tirana, Albania

**Abstract:**
*Nephrocalcinosis (NC) is a rare renal disorder that is increasingly being diagnosed in both children and adults. This study aims to analyze the etiology, presenting complaints, clinical findings, growth and development, renal function at presentation, treatment, and to relate growth and renal function to changes in NC in patients with a follow-up for a period of at least 36 months. Data on 18 children with a US diagnosis of bilateral NC were analyzed. The most frequent causes of NC were hereditary tubulopathy and vitamin D intoxication in childhood in Albania. The treatment of underlying conditions is associated with catch-up growth and stabilization of renal function in many children, but not with reduction in the degree of NC in the majority of cases. Early recognition of conditions leading to NC is clinically useful, and this study provides valuable insights into the diagnosis and management of NC in children. The diagnostic flowchart suggested in this study may be helpful in the approach to NC.*

**Keywords:** Nephrocalcinosis, children, etiology, diagnosis, growth and development, renal function, treatment.

**Introduction:** Nephrocalcinosis (NC) is the deposition of calcium salts in the renal parenchyma and tubules, which may lead to tubular atrophy, interstitial inflammation, and renal function impairment [1]. This disease is rare but has become increasingly diagnosed due to the widespread use of ultrasound (US) in pediatric care [2-3]. NC is usually asymptomatic but in rare cases, it may present with urinary tract infections, hematuria, obstructive uropathy, or renal failure [4-5]. The pathogenesis and etiology of NC are complex and multifactorial. NC can be caused by a variety of inherited or acquired disorders of renal tubular function, calcium or phosphate metabolism, vitamin D metabolism, and other metabolic disorders [6]. The diagnosis is usually made by abdominal US, which shows hyperechoic foci in the renal parenchyma or tubules [7]. The management of NC depends on the underlying cause, and treatment aims to prevent the progression of renal impairment. However, the effect of treatment on the degree of NC is controversial [8-9]. Therefore, the evaluation of children with NC requires a comprehensive approach to the diagnosis and management of the underlying condition. This study aims to provide additional insights into the diagnosis and management of NC in children, which may be useful for clinicians practicing in this area.

**MATERIAL AND METHODS**

Data on patients followed in our unit were retrospectively analysed: the records of 18 children with a US diagnosis of bilateral NC were reviewed at Pediatrics department of the
University Hospital Center "Mother Teresa", in Tirana, Albania, which represents III level referral center for nephrological problems in our country.

Premature infants and neonates treated with furosemide with a diagnosis of NC were not included in the study. The evaluated parameters at the time of presentation for each patient were: clinical manifestations, body height and weight, urinary calcium excretion, glomerular function, renal US. Auxological data were analysed using Tanner / Whitehouse tables, and the height standard deviation score (SDS) was calculated using the standards of Tanner, Whitehouse, and Takaishi [10]. Glomerular function estimated as GFR, calculated by the Schwartz formula, in children older than 1 year (11), and it was considered normal if its value was >80 mL/ min / 1.73 $m^2$; in children younger than 1 year, a table of age specific limits for serum creatinine, as mean ± 3 SD was used. Calciuria was calculated by the urinary calcium / creatinine ratio (Ca / Cr) in second morning urine samples or in mg/ kg / day.

The values of Matos et al. (12) were used as references for the Ca / Cr ratio, and values> 4 mg/ kg / day were considered high in the urine collected within 24 hours. Diagnosis of the most common conditions was made as follows: Drta by a positive urinary gap anion and high urinary pH in the presence of hyperchloremic metabolic acidosis; vitamin D (VD) intoxication by hypercalcemic-hypercalciuria with low levels of parathyroid hormone,high plasma VD levels and corresponding clinical history. Type I hyperoxaluria was confirmed by molecular analysis in the presence of suggestive clinical data and increased plasma oxalate levels. US was performed in the Department of Pediatrics in the Nephrology and Radiology Unit, with 3.5–5 MHz convex probes. Out of 25 patients in total, 18 of them were followed for at least 36 months. Growth, glomerular function and evolution of NC, were analysed at last examination and compared with data at presentation.

**RESULTS AND DISCUSSION Baseline data**

Age of 18 (12 males and 6 females) patients at first examination varied from 15 days to 10 years old (median 15 months). Signs and symptoms which brought children to medical attention were: failure to thrive in first year of life in 67% of children; urinary tract infections, bladder voiding dysfunction or recurrent abdominal pain in 22% of children; a miscellany ofsigns or symptoms was present in 7% of children. NC was detected accidentally in 11% of the cases during screenings or follow-upin congenital syndromes or malformations. 55% of children showed height below the third percentile. Glomerular function was normal in the great majority (83%) of patients, two children suffered from renal insufficiency (GFR from
24 and 68 mL/ min / 1.73 $m^2$) and one 10 years old child was accidentallydiagnosed only at presentation with terminal renal failure. Hypercalciuria was found in 44% of patients. In 61% of children, NC was associated with hereditary tubulopathy and in 11% of cases secondary to VD intoxication. Other causes and details are shown in Table 1.In 11% of children the cause of NC remained unknown. NC was classified as medullary in 89% of patients and global in 11%. Global NC was detected in two children: one suffered from terminal renal failure and the other from oxalosis. **Follow-up**

Data of 18 / 25 patients (12 males and 6 females) followed for at least 36 months were analyzed:detailed diagnosis arerepresented in Table 1. In these patients, SDS for height improved from a median value of -2.2 (range -6.8. +1.1) to a median value of -1.0 (range -3.2 / +2.4) at the end offollow-up. Heigh was below -2.0 SDS in 54% of children at presentation and in 22% at last investigation. Among the 11 patientswhose growth improved, there were 7 / 8 children with dRTA, Bartter syndrome and Dent disease. None of the patients had been treated with growth hormone at any time during follow-up. In 7 / 18 children >1 year old GFR was decreased in 57%atpresentation and in 14% at follow-up. In particular, remarkable improvement of glomerular function was observed in one child with VD intoxication, after withdrawal of the drug, and in one child who suffered from Dent disease after stone removal; a decreasing GFR was confirmed and remained so only in the patientsuffering from terminal renal failure.

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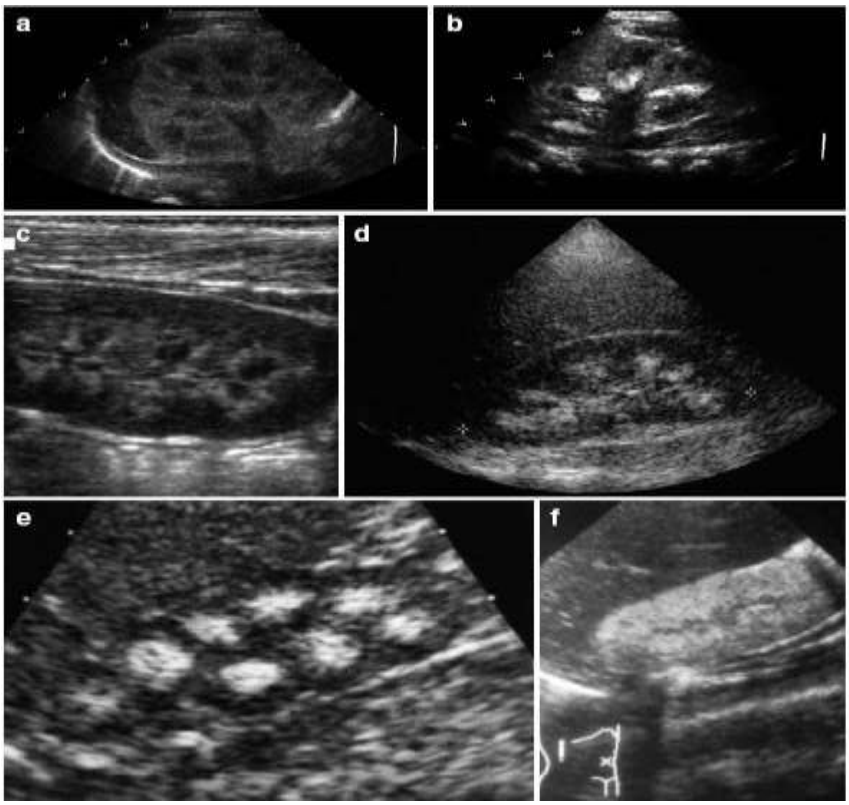
The degree of NC (follow-up for 18 patients) worsened in 9 patients (50%), remained stable in 5 (28%) and decreased in 4 patients (22%). In particular, NC worsened in children with Bartter syndrome and Dent disease in whom growth was improved; the same was true for 4 / 8 patients with dRTA. Of the four children in whom improvement of NC was observed, two suffered from dRTA, one from VD intoxication and the other one from an unknown cause. We found no relation between glomerular function and worsening of NC, as GFR remained stable in 17 / 18 patients showing progression of NC.

**Table1**. Underlying conditions in children with NC at baseline and at follow-up

| **Condition** | **No. of patients** | **No. of patients with follow-up>36 months** |
|---|---|---|
| Distal renal tubular acidosis | 11 | 8 |
| Other hereditary tubulopathies:<br>Bartter syndrome<br>Dent disease | 3<br>1<br>1 | 3<br>1<br>1 |
| Hyperoxaluria type I | 1 | 1 |
| Idiopathic hypercalciuria | 2 | 2 |
| Vitamin D intoxication | 4 | 4 |
| Hypercalcemia with hypercalciuria | 1 | 1 |
| Unknown | 4 | 2 |
| Total | 25 | 18 |




The results of this study have been gathered retrospectively from the records of Pediatric Nephrology Department, located in the University Hospital Center of Tirana "Mother Teresa", which represents III level referral center for nephrological problems in our country. AsNC is an uncommon disease, which is not usually looked after by general pediatric departmentsin our country and is therefore referredin our center, we expect that the spectrum of diagnoses, in our cohort of children, reflects the epidemiology of NC of the area.

Urinary tract infections, bladder voiding dysfunction or abdominal pain also brought children to medical attention. To the best of our knowledge, clinical manifestations and especially somatic and psychomotor development had not been examined in significant studies in children with NC detected by US until the study of Rönnefarth et al. [8].In this study, growth failure, psychomotor and mental retardation were found in a high percentage of patients; in particular, height below the lower normal limit was detected at presentation in 41% of 72 children older than 1 year. In addition, more than one third of their patients suffered from urinary tract infections. Growth improved during clinical follow-up in 61% of children in our study, especially in patients with dRTA, Bartter syndrome, and Dent disease.In the German study [8], significant growth improvement was only observed in patients with IH, but a relative improvement was also stated in some patients suffering from tubular disorders as well as in patients who had received bolus prophylaxis or prolonged VD therapy. In the Indian study, most patients continued to show growth retardation and GFR declined by 15% after a median follow-up of approximately 35 months [9]. Glomerular function was normal in most of our cases, except for three children; one with oxalosis, another with Dent disease and the third one showed global NC and was interminal renal failure at first examination. In the case of global NC, a rare ultrasound parameter often related to oxalosis, the search for this conditionappears mandatory.

Our follow-up data on GFR in patients older than 1 year of age are similar to those of Rönnefarth et al, who found that 43% (3 of 7 patients suffering from renal insufficicieny) had a GFR less than 80 mL/ min/ 1.73 $m^2$ at

presentation and 29% at last investigation. Therefore, improvement of GFR can be expected after an accurate diagnosis and correct treatment of the cause of NC. Our experience also shows that, unless the patients hasoxalosis or Dent disease, and provided acute insults are removed, prognosis concerning glomerular function in children with NC is good. Regression of NC should not be expected; on the contrary, worsening of NC during follow-up by US was a common finding both in our and Rönnefarth's studies, most of the cases being represented by hereditary tubulopathies. However, the available follow-up data on persistance or even progression of NC, do not present a negative prognostic factor for growth and renal function. It is not beneficial to continue describing drug induced NC in every study [5-9]; it is often secondary to VD intoxication or treatment, especially in countries where bolus administration of high doses has been used.In our study, four patients developed NC, which was permanent in two, after hypercalcemic-hypercalciuria due to VD treatment. Therefore, the high risk of bolus VD prophylaxis and the need for careful controls of calciuria during substitutive therapy should be acknowledged. IH was an exceptional cause of NC in our study, since it was only detected in two patients, who also presented with renal stones during their infancy. A low incidence of IH as a cause of NC was also stated in previous studies [5–7]; the German study is an exception [11], in which IH was found to be the main cause of NC, representing 34% of cases. The cause of NC could not be identified in four of our patients, two of them having been lost to follow up. In some of these cases, the diagnosis of medullary sponge kidney may have been missed, as an intravenous pyelography was not performed routinely in NC of unknown origin [12]. From the review of the clinical history and the results of the diagnostic procedures of the patients evaluated in this retrospective study and from the review of the available literature, we have produced two diagnostic flowcharts, which may be helpful in the clinical approach to NC in children.

**CONCLUSION**

In conclusion, our results show that treatment of the underlying conditions is assocciated with catch-up growth and stabilisation of glomerular function in many children with NC. We therefore believe that early recognition of conditions leading to NC is clinically useful. Treatment, however, does not reduce the degree of NC in the majority of cases; therefore NC seems to be an epiphenomenon having little influence on the clinical course.

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