Nephrocalcinosis and Nephrolithiasis in X-Linked Hypophosphatemic Rickets: Diagnostic Imaging and Risk Factors

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Context: Nephrocalcinosis (NC) and nephrolithiasis (NL) are described in hypophosphatemic rickets, but data regarding their prevalence rates and the presence of metabolic risk factors in X-linked hypophosphatemic rickets (XLH) are scarce.

Objective: To determine the prevalence rates of NC and NL and their risk factors in patients with XLH with confirmed PHEX mutations.

Methods: Renal ultrasonography (US) and CT were performed in 16 children and 23 adults. The images were evaluated by two blinded radiologists specializing in US and two specializing in CT. Confirmation of NC was determined with a positive result on both US and CT, whereas the diagnosis of NL was confirmed by CT alone. The presence of hypercalciuria, hypocitraturia, and hyperoxaluria was determined from 24-hour urinary samples from each patient. The glomerular filtration rate was estimated.

Results: NC was identified in 15 patients (38.4%), and stratification by age group showed a higher prevalence of NC in children than in adults (56.2% vs 26.1%). CT identified NL in four adults (10.2%). Patients in the pediatric group required intensive use of phosphate, started treatment earlier, and presented greater phosphaturia than those in the adult group (P < 0.01). In addition to hyperphosphaturia, which was present in all patients with XLH, hypocitraturia was the most common metabolic factor (28.2%), whereas hypercalciuria occurred in two patients (5.1%). None had hyperoxaluria. Most patients had normal renal function.

Conclusions: NC was more prevalent than NL. The main metabolic factor was hyperphosphaturia, and intensive phosphate treatment appears to be a worsening factor for kidney calcification.

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Freeform/Key Words: heritable hypophosphatemic rickets, XLH, PHEX, nephrocalcinosis, nephrolithiasis

Abbreviations: ALP, total alkaline phosphatase; FGF, fibroblast growth factor; GFR, glomerular filtration rate; NC, nephrocalcinosis; NL, nephrolithiasis; US, ultrasonography; XLH, X-linked hypophosphatemic rickets.
Renal calcification disorders include two distinct conditions: nephrocalcinosis (NC), which involves calcium deposition in the renal parenchyma, and nephrolithiasis (NL), which involves calcification within the collecting system [1]. Both diseases have several risk factors, such as a positive family history of kidney stones, anomalies of the urinary tract predisposing to urinary tract infections, the use of medications, and the presence of metabolic diseases [2].

The most common metabolic disorder in patients diagnosed with NC is hypercalciuria [3, 4]. Hypocitraturia, hyperoxaluria, and hypercalciuria are the main metabolic abnormalities in patients with NL [2, 5, 6]. Hyperphosphaturia is also an independent risk factor for the development of renal calcification [7, 8].

Hyperphosphaturia and resultant hypophosphatemia are caused by a pathological increase in serum levels of fibroblast growth factor 23 (FGF23) in patients with X-linked dominant hypophosphatemic rickets (XLH) (OMIM 307800); this abnormality is determined by inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) [9]. Thus, patients with XLH are at risk for developing renal calcification, mainly during treatment with phosphate salts and calcitriol.

In most cases of NC and NL, diagnostic imaging including renal ultrasonography (US) and computed tomography (CT) can provide helpful data to optimize surveillance and prevent complications [1, 3, 5, 10]. In patients with XLH with identified disease-causing PHEX mutations, data regarding the evaluation of renal calcifying disorders with US and CT that include an analysis of metabolic disorders are scarce. Thus, the aim of this single-center study was to determine the prevalence of NC, NL, and their metabolic risk factors in a group of 39 patients with XLH with confirmed PHEX mutations.

1. Materials and Methods

A. Subjects

The study protocol was approved by the Ethics Committee of the Hospital das Clínicas da Universidade de São Paulo (CAPesq HCFMUSP), and informed consent was obtained from all patients and control subjects or their parents.

All patients were monitored by the Osteometabolic Diseases Unit of the HCFMUSP. The patients were selected based on their medical history and the results of physical examinations and laboratory and radiological findings consistent with XLH. At the time of diagnosis, all patients presented with hypophosphatemia and hyperphosphaturia (fractional excretion of phosphate >5% [11]), high serum levels of FGF23, and high serum total alkaline phosphatase (ALP) levels. Patients with tumor-induced osteomalacia and other renal tubulopathies were excluded from the study.

Forty-seven patients fulfilled these criteria, but only 39 patients (age 3 to 76 years; 16 children and 23 adults; 30 women and 9 men) who presented disease-causing PHEX mutations, as determined by Sanger sequencing and multiplex ligation-dependent probe amplification analysis, were included in this study. They were followed for 5 years at regular intervals depending on the intensity of treatment: children were followed every 4 months, and adults were followed every 6 months.

At the time of the study, all 16 children with XLH (3 to 18 years old) were actively being treated with phosphate salts (30 to 60 mg/kg/d) and calcitriol (15 to 60 ng/kg/d). They were evaluated regarding growth velocity, radiological signs of rickets, and ALP levels (data not shown).

Of the 23 adult patients with XLH (23 to 76 years old), only two patients used phosphate during the study in adulthood, and all patients were taking calcitriol, seven of whom started using it during the study. All cases of vitamin D insufficiency were promptly corrected.

B. Diagnostic Imaging

Diagnostic imaging was performed at the end of the follow-up period for each patient for cross-sectional analysis. Renal US was performed using an LOGIQ E9 with an XDclear...
Ultrasound system (General Electric Company, Fairfield, CT) and a iU22 Ultrasound system (Philips Health Care, Andover, MA). Multislice CT was performed using a CT Brilliance 64 scanner (Philips Health Care, Cleveland, OH) and an Aquilion 64 scanner (Toshiba Medical Systems, Otawara, Japan). All examinations were performed at the Radiology Institute at the HCFMUSP.

Two radiologists with expertise in US and two other radiologists with experience in CT evaluated the images for both NC and NL. They were blinded to the patient’s diagnosis, and each radiologist interpreted his respective modality independently. One of the radiologists performed a dynamic US study, and the other analyzed a series of recorded US images. They classified the NC results according to the grading system proposed by Boyce et al. [1]. The US grades were as follows: grade 0, no echogenicity; grade 1, mild echogenicity around the medullary pyramid borders; grade 2, moderate echogenicity around and inside the pyramids; and grade 3, severe echogenicity of the entire pyramidal area. The CT grades were as follows: grade 0, no calcific deposits; grade 1, one to three pyramidal punctate calcifications; grade 2, increased pyramidal density; and grade 3, calcification of pyramids. In both methods, the presence of involved papillae yielded a score >0; no minimal number of papillae was required. When features of multiple grades were present or the extent of disease differed between the two kidneys, the higher score was assigned. To improve specificity and promote a more accurate diagnosis of NC, NC was diagnosed only when positive results were found on both US and CT [3], whereas the diagnosis of NL was confirmed by CT [6].

C. Biochemistry

Blood and urinary samples from all patients were collected and analyzed throughout the follow-up period.

Blood samples from the patients were drawn between 7 AM and 9 AM after an overnight fast. Serum levels of calcium, phosphate, creatinine, and ALP were measured using standard laboratory methods. FGF23 concentrations were measured using an intact human FGF23 ELISA [12] (Kainos Laboratories, Tokyo, Japan), procollagen type-1 N-terminal propeptide [13] was measured by an automated electrochemiluminescence system (E411; Roche Diagnostics, Mannheim, Germany), parathyroid hormone levels were measured by a parathyroid hormone assay [14] (Immulex 2000 Intact; DPC, Los Angeles, CA), and 25-hydroxyvitamin D values were measured by radioimmunoassay (DiaSorin Corporation, Stillwater, MN).

In children and adolescents, the glomerular filtration rate (GFR) was estimated by the Schwartz equation [15], and the Chronic Kidney Disease Epidemiology Collaboration formula was used in adults. Normal GFR was defined as >90 mL/min per 1.73 m² [16].

The 24-hour urine samples were collected to simultaneously analyze calcium (normal range, 1.5 to 4.0 mg/kg), phosphate, and creatinine every 4 months for children and every 6 months for adults. The mean values of at least three samples were calculated for each patient.

At least two 24-hour urine samples were collected from each patient to measure citrate (normal range >365 mg/1.73 m² for male patients and >310 mg/1.73 m² for female patients) and oxalate (normal range up to 45 mg/1.73 m²) [2].

D. Statistical Analysis

The data were expressed as the mean ± SD, and comparisons between groups were performed using independent unpaired Student t test. Associations between categorical variables and groups were assessed with the χ² test and Fisher exact test when appropriate. A P value <0.05 was considered statistically significant. The weighted kappa statistic was used to summarize the interobserver agreement for each imaging modality with 95th percentile confidence limits. Statistical analysis was performed with the Statistical Package for the Social Sciences software for Windows version 20.0 (SPSS Inc., Chicago, IL).
2. Results

US diagnosed NC in 37 patients with XLH (94.9%): 36 patients had grade 1 NC, and one child had grade 2 NC. All of the children (100%) and 21 adults (91.3%) had NC diagnosed by US. The interobserver agreement was moderate for US, with a weighted kappa statistic of 0.597 (95% CI, 0.359 to 0.835). In addition, CT identified medullary NC in 15 patients (38.5%): 10 had grade 1 NC, and five had grade 2 NC; none of them presented cortical NC. According to CT, nine children (56.2%) and six adults (26.1%) had NC (Fig. 1). Agreement was found to be very poor when the comparison was performed between US and CT, with a weighted kappa statistic of only 0.065 (95% CI, −0.027 to 0.157).

Although US is more sensitive than CT, particularly for the detection of early-stage NC, results based only on positive US findings may overestimate the prevalence of NC [1]. Furthermore, in our cohort, if we consider NC based only on US findings, then evaluating metabolic risk factors and potential differences between the age groups would not be possible because all of the children (100%) and 21 adults (91.3%) had NC diagnosed by US. Therefore, we considered NC diagnosis when both US and CT were positive even though the real prevalence of NC should be underestimated with this approach. According to this criterion and stratification by age group, children showed a higher prevalence of NC than adults (56.2% vs 26.1%; \( P = 0.05 \)) (Fig. 2). Moreover, CT identified NL in only four adults (10.2%), two of whom also had NC (Fig. 3).

At the time of the study, all the children were being treated with phosphate salts, whereas only two adults were taking phosphate salts. In the adult group, 14 of 23 patients had received phosphate treatment during childhood, but they had a later onset of treatment than those in the pediatric group (8.0 ± 3.2 years vs 2.8 ± 2.3 years; \( P < 0.01 \)). Most of them had irregularly used the medication and used a lower dosage of phosphate than the dosage that is used currently (data not shown). There was no difference between the age groups in terms of the duration of phosphate treatment during childhood (8.3 ± 4.6 years vs 11.5 ± 4.4 years;
Furthermore, adults with XLH were shorter than children with XLH (z score for height, $-3.4 \pm 1.5$ vs $-2.4 \pm 1.4$; $P < 0.05$) (Table 1).

The pediatric group had greater phosphaturia than the adult group ($24.1 \pm 12.9$ vs $8.2 \pm 2.5$ mg/kg/d; $P < 0.01$), but no difference was found between age groups in terms of tubular maximum reabsorption of phosphate per unit of glomerular filtrate ($P = 0.15$) or tubular reabsorption of phosphate ($P = 0.43$) (Table 1).

In addition to hyperphosphaturia, 12 of the 39 studied patients (30.8%) had other metabolic factors diagnosed in more than one 24-hour urinary sample. Hypocitraturia was the most common in both age groups (five children and six adults), whereas hypercalciuria occurred in only two patients (one child and one adult). Only one adult had both hypercalciuria and hypocitraturia. None of the patients had hyperoxaluria. There was no difference between age groups in terms of the presence of hypercalciuria ($P = 0.99$) or hypocitraturia ($P = 0.73$).

Although hypocitraturia and hypercalciuria were identified in the studied patients, no differences were observed between the groups with and without NC (Table 2).

Two of seven studied families presented members with NC diagnosed by both methods. In the first family consisting of five affected members, the father and the two young daughters had NC. None of them had metabolic factors other than hyperphosphaturia. In the second family with two affected members, the mother and her young son had NC, hypercalciuria, and hypocitraturia. The mother developed tertiary hyperparathyroidism and presented with NL.

Two other elderly patients developed tertiary hyperparathyroidism at 55 years and 58 years during the follow-up, one of whom exhibited NC. Parathyroidectomy was performed successfully in these three patients.

Despite the great prevalence of NC, most of the patients had normal kidney function. Two elderly patients had decreased GFR that was stage 2 according to the Kidney Disease: Improving Global Outcomes CKD Work Group [16]. One of them suffered from poorly controlled hypertension and NC diagnosed by US, and the other had NC diagnosed by US and CT.

![Figure 2. The prevalence of NC diagnosed by both renal US and CT in 39 patients with XLH stratified by age group.](https://academic.oup.com/jes/article-abstract/3/5/1053/5418933/1057)
3. Discussion

Despite using a strict criterion for the imaging diagnosis of NC and considering that the true prevalence of NC is underestimated in this study, our cohort with 39 patients with XLH presented a high prevalence of NC (38.5%), and most of the patients had minor grades of calcification and normal glomerular function. Therefore, the severity of NC seemed to be mild without major complications. Regardless of the low prevalence of NL (10.2%) compared with that of NC, kidney calcifications were more prevalent in our cohort compared with the general population [6].

Previous reports have yielded conflicting results about the preferred imaging modality for the assessment of NC [1, 3, 10, 17]. In experimental studies with rabbits, Cramer et al. [10] compared renal US and renal CT results with pathological analysis. US was more sensitive than CT (96% vs 64%), whereas CT was more specific than US (96% vs 85%). Cheidde et al. [3] reported that an improved sensitivity and specificity were achieved for the diagnosis of NC with CT performed in association with US or X-ray. Moreover, low agreement between US and CT can be explained by the ability of small reflectors, such as small calcific aggregations, to act as strong scatterers of ultrasound waves. The density of calcification early in the course of NC may not be sufficient for detection by CT, thus rendering US more sensitive [1].

Although our strategy failed to diagnose early NC, it allowed us to compare patients with confirmed NC with the remaining patients to identify metabolic risk factors for NC pathogenesis. Despite its high sensitivity, when considering only US as a diagnostic method, the prevalence of NC may be overestimated.

In our trial, the pediatric group had a higher prevalence of NC than the adult group. This difference may be explained by the greater phosphaturia present in the pediatric group due to an earlier onset of phosphate treatment and a higher phosphate dosage than the adult group. Furthermore, most of the adults had received irregular phosphate treatment with a low dosage of phosphate during childhood, which had a negative impact on their final height. This
irregular treatment may have contributed to the lower prevalence of NC in this group. On the other hand, four adults who did not take phosphate during childhood developed NC. This finding suggests the impact of the disease on the development of NC in patients with XLH.

Ha et al. [18] considered hyperphosphaturia to be an independent risk factor for NC and NL. Additionally, Cramer et al. [19] showed that the severity of NC was directly proportional to oral phosphate intake in their study with rabbits. Despite the increased development of NC due to hyperphosphaturia, intensive phosphate treatment optimized height outcomes with improvements in skeletal deformities [20]. Moreover, tertiary hyperparathyroidism is also a complication of increased phosphate use and contributes to the development of NC and NL [9].

In our cohort, hypercalciuria was uncommon, and hyperphosphaturia was the primary metabolic factor involved. Hypocitraturia was considered an aggravating element, and hyperoxalaturia was not detected.

In other cohorts involving XLH, hypercalciuria was considered the main metabolic factor for the development of NC during treatment [21, 22], but these prior studies had heterogeneous samples without confirmed disease-causing PHEX mutations as well as patients with other tubulopathies, and different criteria to detect NC were considered. None of the children had NL. This finding may suggest a lower influence of hyperphosphaturia on the development of NL in children. On the other hand, two of four adults with NL had hypocitraturia, and one of them also had hypercalciuria. This finding indicates that these metabolic risk factors cannot be excluded in the genesis of NL. Moreover, all of these patients had normal kidney function, which may indicate a benign course of renal calcifications.

Strengths of our study were the large sample size and homogeneity of the sample due to molecular analysis and follow-up in a single center. Previous trials had smaller and heterogeneous groups with patients with other tubulopathies included because PHEX mutations were not confirmed in the patients. This study was reinforced by the use of two different

### Table 1. Demographic, Laboratorial, and Clinical Data of the Study Population Stratified by Age Group

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (female/male)</td>
<td>16 (12/4)</td>
<td>23 (18/5)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>11.7 ± 5.2</td>
<td>41.9 ± 15.3</td>
<td></td>
</tr>
<tr>
<td>z score of height</td>
<td>−2.4 ± 1.4</td>
<td>−3.4 ± 1.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PTH (NR: 15–65 pg/mL)</td>
<td>78.4 ± 37</td>
<td>64.5 ± 33.1</td>
<td>0.27</td>
</tr>
<tr>
<td>FGF23 (NR: 10–50 pg/mL)</td>
<td>132.3 ± 53.8</td>
<td>85.4 ± 26.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine P/Cr ratio</td>
<td>1.62 ± 0.69</td>
<td>0.56 ± 0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phosphaturia, mg/kg/d</td>
<td>24.1 ± 12.9</td>
<td>8.2 ± 2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TRP</td>
<td>78.8 ± 8.5</td>
<td>81.2 ± 10.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Age at treatment initiation, y</td>
<td>2.8 ± 2.3</td>
<td>8.0 ± 3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of phosphate treatment, y</td>
<td>8.3 ± 4.6</td>
<td>11.5 ± 4.4</td>
<td>0.64</td>
</tr>
<tr>
<td>Phosphate treatment during childhood, n</td>
<td>16/16</td>
<td>14/23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phosphate dosage, mg/kg/d</td>
<td>30–60</td>
<td>Not available</td>
<td></td>
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<tr>
<td>Calciotriol treatment during childhood, n</td>
<td>16/16</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Calciotriol dosage, ng/kg/d</td>
<td>15–60</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Tertiary hyperparathyroidism, %</td>
<td>None</td>
<td>3/23 (13%)</td>
<td></td>
</tr>
<tr>
<td>Presence of NC, %</td>
<td>9/16 (56.2%)</td>
<td>6/23 (26.1%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Family history of NC, %</td>
<td>5/16 (31.3%)</td>
<td>4/23 (17.4%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Presence of NL, %</td>
<td>None</td>
<td>4/23 (17.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD as appropriate. P represents the significance of the differences between the pediatric and adult groups. A P value <0.05 was considered statistically significant.

Abbreviations: Cr, creatinine; NR, normal range; P, phosphate; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate per unit of glomerular filtrate; TRP, tubular reabsorption of phosphorus.

*Children adjusted for age; adults compared as Bijvoet pairs.
imaging methods to diagnose NC and by the gradation in an XLH group. Our limitations were the cross-sectional design and the lack of power to evaluate possible sex differences because of the small number of male patients. Moreover, as in the study by Boyce et al. [1], renal biopsies, which are the gold standard of diagnosis, were not available to confirm the presence or absence of NC, but positive findings on both imaging examinations in a high-risk population were assumed to be indicative of a definitive diagnosis.

The use of novel therapeutic strategies for XLH, such as anti-FGF23 monoclonal antibody (burosumab), will change the natural history of NC and NL in patients with XLH and confirm the role of inherent hyperphosphaturia in the development of renal calcification [23].

In summary, in our cohort, the main metabolic risk factor for the development of NC was hyperphosphaturia, and intensive phosphate treatment appears to be an aggravating factor. Hypocitraturia and hypercalciuria may be involved in the genesis of NL. Despite the considerable prevalence of NC and NL, the presence of normal kidney function in most of our patients with XLH suggests a benign course of these renal calcifications.

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Disclosure Summary: The authors have nothing to disclose.

Table 2. Demographic, Laboratory, and Clinical Data of the Study Population Stratified by the Presence of Nephrocalcinosis and/or Nephrolithiasis

<table>
<thead>
<tr>
<th></th>
<th>With NC and/or NL</th>
<th>Without NC and/or NL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (female/male)</td>
<td>17 (13/4)</td>
<td>22 (17/5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Age, y</td>
<td>25.8 ± 19.7</td>
<td>32.4 ± 19.6</td>
<td>0.05</td>
</tr>
<tr>
<td>z score of height</td>
<td>−2.46 ± 1.49</td>
<td>−3.39 ± 1.40</td>
<td>0.18</td>
</tr>
<tr>
<td>PTH (NR: 15–65 pg/mL)</td>
<td>60.7 ± 23.6</td>
<td>76.4 ± 39.2</td>
<td>0.24</td>
</tr>
<tr>
<td>FGF23 (NR: 10–50 pg/mL)</td>
<td>119.5 ± 61.7</td>
<td>97.8 ± 33.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Cr</td>
<td>0.50 ± 0.18</td>
<td>0.54 ± 0.16</td>
<td>0.32</td>
</tr>
<tr>
<td>TRP</td>
<td>160.0 ± 53.6</td>
<td>145.0 ± 37.5</td>
<td>0.72</td>
</tr>
<tr>
<td>z score of height</td>
<td>2.46 ± 6</td>
<td>1.49 ± 2</td>
<td>0.05</td>
</tr>
<tr>
<td>PTH (NR: 15–65 pg/mL)</td>
<td>60.7 ± 23.6</td>
<td>76.4 ± 39.2</td>
<td>0.24</td>
</tr>
<tr>
<td>FGF23 (NR: 10–50 pg/mL)</td>
<td>119.5 ± 61.7</td>
<td>97.8 ± 33.2</td>
<td>0.54</td>
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<tr>
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<td>0.54 ± 0.16</td>
<td>0.32</td>
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<tr>
<td>TRP</td>
<td>160.0 ± 53.6</td>
<td>145.0 ± 37.5</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± SD as appropriate. P represents the significance of the differences between the pediatric and adult groups. A P value <0.05 was considered statistically significant.

Abbreviations: Cr, creatinine; NR, normal range; P, phosphate; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphorus.

References and Notes


