NEPHROCALCINOSIS AND NEPHROLITHIASIS IN 36 X-LINKED HYPOPHOSPHATEMIC RICKETS PATIENTS: DIAGNOSTIC IMAGING AND EVALUATION OF RISK FACTORS IN A SINGLE-CENTER STUDY

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BACKGROUND

Renal calcifying disorders include two distinct conditions: **nephrocalcinosis (NC)** that describes the renal parenchyma calcium deposition and **nephrolithiasis (NL)** that comprises the calcification within the collecting system.

The most common metabolic disorders in patients diagnosed with NC and NL are hypercalciuria, hypocitraturia and hiperoxaluria, but **hyperphosphaturia** is also an independent risk factor.

Hyperphosphaturia and resulting hypophosphatemia due to a pathological increase in the FGF23 levels characterize the **X-linked dominant hypophosphatemic rickets (XLH)**, which is determined by inactivating mutations in *PHEX* gene. Although this group is at risk to develop renal calcifications, the data about these conditions are scarce in XLH patients with confirmed disease-causing *PHEX* mutations.

AIM

To determine the prevalence of NC, NL and their risk factors in XLH patients, followed in a single center, with confirmed *PHEX* mutations.

PATIENTS AND METHODS

- 36 patients (**15 children and 21 adults**; 27 women and 9 men), with *PHEX* mutations determined by Sanger and MLPA methods, were followed for 5 years at regular intervals.
- 24h urinary samples were collected and their chemical analysis included **creatinine**, **calcium**, **citrate**, **oxalate** and **phosphate**. It was determined the number of episodes of hypercalciuria, hypocitraturia and hyperoxaluria for each patient.
- In children and adolescents, the **GFR** was estimated by the Schwartz formula, while the Cockroft-Gault equation was used in adults. Normal GFR was defined as > 90 ml/min per 1.73 m^2.
- **Renal ultrasonography (US)** was performed by GE LOGIQ E9 with XDclear Ultrasound system and the Phillips iU22 Ultrasound system devices while **multislice computed tomography (CT)** was performed by Philips CT Brilliance 64 channel and the Toshiba Aquilion 64 channel devices.
- Two blinded radiologists graded NC using a 0–3 scale with 0 meaning no NC and 3 meaning severe NC. The NC confirmation was determined with a positive result in both US and CT while the NL diagnosis was confirmed by CT.
- The comparison between groups was performed using the independent unpaired Student's t test or Mann-Whitney U test. Frequencies of categorical variables were compared with the Fisher exact test where appropriate. *p* values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

- Demographic and clinical features of the study population are presented in **table 1** and the biochemical findings are shown in **table 2**.

Table 1. Descriptive characteristics and phosphate treatment data of the study population

	All patients	Children	Adults	*p*
n (female/male)	36 (27/9)	15 (11/4)	21 (16/5)	
Age (y)	29.3 ± 19.3	11.7 ± 5.2	41.9 ± 15.3	
Height (SD)	-2.96 ± 1.50	-2.42 ± 1.45	-3.34 ± 1.45	<0.05
Phosphate treatment during childhood (n)	32	15	17	0.07
Age of phosphate onset (y)	5 [1;49]	2 [1;9]	9 [3;49]	0.01

Values are expressed as the mean ± SD or median [minimum; maximum] as appropriate; *p* represents the significance of the differences between the children and adult groups; $p < 0.05$ was considered statistically significant.

Table 2. Biochemical findings of the study population

	All patients	Children	Adults	*p*
GFR (ml/min/1.73 m^2)	152.6 ± 47.3	186.4 ± 44.4	128.4 ± 32.5	
Urinary phosphate (mg/kg/d)	15.03 ± 11.87	24.48 ± 13.36	8.28 ± 2.64	<0.01
Number of patients with hypocitraturia	11 (30.5%)	5 (33.3%)	6 (28.5%)	0.76
Number of patients with hypercalciuria	2 (5.5%)	1 (6.6%)	1 (4.7%)	1.0

Values are expressed as the mean ± SD. *p* represents the significance of the differences between the children and adult groups; $p < 0.05$ was considered statistically significant.

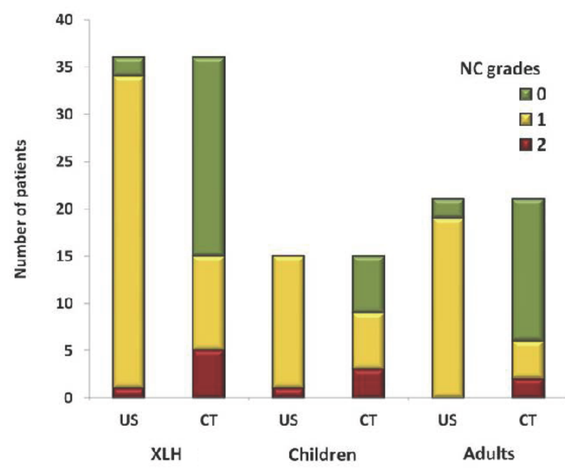

Figure 1. Distribution of NC grades according to the renal US and CT results in 36 XLH patients stratified by age group.

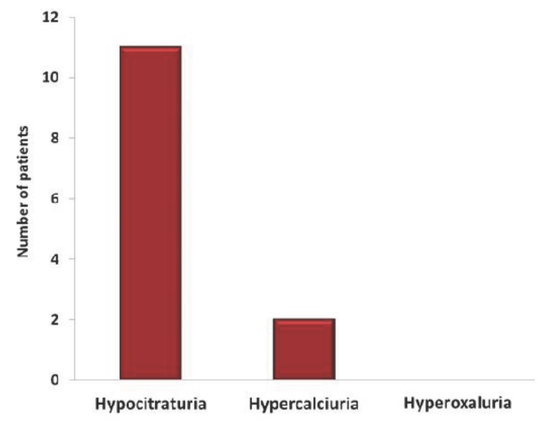

Figure 3. Distribution of metabolic risk factors in 36 XLH patients.

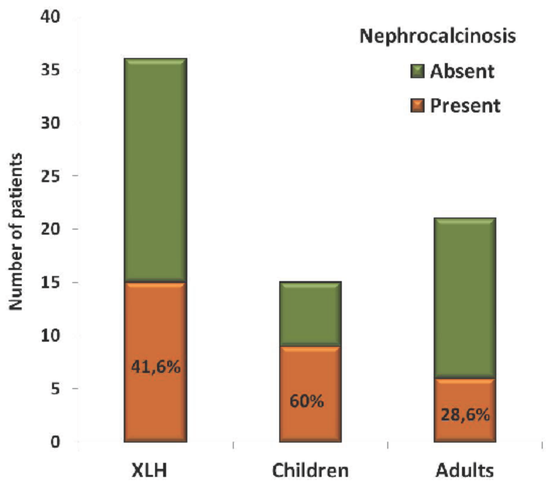

Figure 2. Prevalence of NC diagnosed by both renal US and CT in 36 XLH patients stratified by age group.

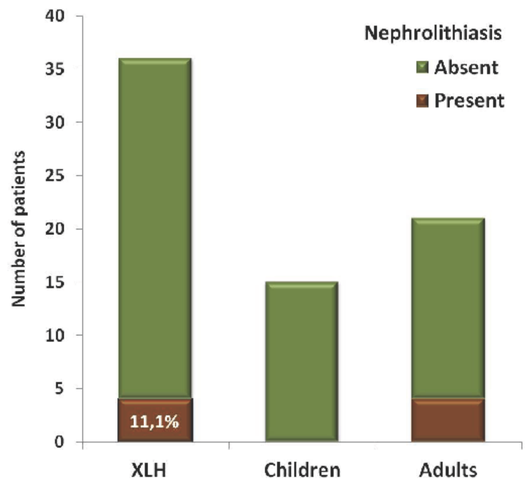

Figure 4. Prevalence of NL based on renal CT findings in 36 XLH patients stratified by age group.

- The US analysis identified, mainly, the NC grade 1 due to its higher sensibility, while the CT showed a major proportion of NC grade 2 because of its greater specificity (**figure 1**). In order to improve the sensibility and specificity of NC diagnosis, in our cohort, NC confirmation was only determined with a positive result in both US and CT (**figure 2**).
- In our cohort, surprisingly, children had a higher prevalence of NC than the adults (60% *vs* 28.6%) – **figure 2**. This difference may be explained by the greater phosphaturia in the pediatric group due to an earlier onset of phosphate treatment and a higher phosphate dosage compared to the adults group – **tables 1** and **2**.
- In the adults, most of them had an irregular phosphate treatment and they used a lower dosage of phosphate during their childhood with negative impact on their final height (**table 1**). This irregular treatment may have contributed to a lower prevalence of NC in this group. On the other hand, four adults, who did not use phosphate in childhood, had NC. It suggests the impact of the disease in NC development in XLH patients.
- Although hypocitraturia and hypercalciuria were identified in the studied patients (**figure 3**), no differences were observed between the groups with and without NC (data not shown).
- Regardless of the minor prevalence of NL compared to NC (11.1% *vs* 41.6%; **figures 2** and **4**), both of kidney calcifications were more prevalent than general population.
- None of the children had NL (**figure 4**). It may suggest a lower influence of hyperphosphaturia in NL development. On the other hand, two of four adults with NL had hypocitraturia and one of them had also hypercalciuria. It indicates that these metabolic risk factors cannot be excluded in the NL genesis.
- Most of the patients had normal kidney function which may indicate a benign course of the renal calcifications.

CONCLUSIONS

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

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