Hypertension is a characteristic complication of X-linked hypophosphatemia

Yoshie Nakamura¹, Masaki Takagi², Ryojun Takeda³, Kentaro Miyai² and Yukihiro Hasegawa¹, ²

¹ Division of Genetic Research, Tokyo Metropolitan Children’s Medical Center, Tokyo 183-8561, Japan
² Division of Endocrinology and Metabolism, Tokyo Metropolitan Children’s Medical Center, Tokyo 183-8561, Japan
³ Division of Pediatrics, Keio University School of Medicine, Tokyo 160-8582, Japan
⁴ Division of Medical Genetics, Tokyo Metropolitan Children’s Medical Center, Tokyo 183-8561, Japan

Abstract. X-linked hypophosphatemia (XLH) is a group of rare disorders caused by defective proximal tubular reabsorption of phosphate. Mutations in the PHEX gene are responsible for the majority of cases. There are very few reports of long-term complications of XLH other than skeletal and dental diseases. The aim of this study was to identify the phenotypic presentation of XLH during adulthood including complications other than skeletal and dental diseases. The clinical and biochemical phenotype of 22 adult patients with a PHEX gene mutation were examined retrospectively from their medical records. 6 patients had hypertension. The average age of hypertension onset was 29.0 years. Secondary hyperparathyroidism preceded the development of hypertension in 5 patients. 1 patient developed tertiary hyperparathyroidism. 15 patients had nephrocalcinosis. 2 patients had chronic renal dysfunction. Patients with hypertension had a significantly lower eGFR (p=0.010) compared to patients without hypertension. No significant difference was found in any other parameters. To examine the genotype-phenotype correlation, 10 adult males were chosen for analysis. No significant genotype-phenotype correlation analysis was revealed in any of the complications. However, there was a possibility that the age at nephrocalcinosis onset was younger in the non-missense mutation group than in the missense mutation group (p=0.063). This study corroborated the view that early-onset hypertension could be one of the characteristic complications seen in XLH patients. Considering the limited number of our patients, further study is necessary to address a potential cause of hypertension. XLH patients require careful lifelong treatment.

Key words: Hypophosphatemic rickets, X-linked hypophosphatemia, PHEX, Hyperparathyroidism, Hypertension

X-LINKED HYPOPHOSPHATEMIA (XLH) is a disorder of the mineralization of the bone matrix caused by defective proximal tubular reabsorption of phosphate, and a defect in renal 25-hydroxyvitamin D 1α-hydroxylase activity. XLH is a rare disease, with an incidence of 3.9 per 100,000 live births and a prevalence of 4.8 per 100,000 (0–14.9 years) [1]. Mutations in the PHEX gene are responsible for the majority of cases. At the biological level, XLH is characterized by low renal phosphate reabsorption, a normal serum calcium level without hypercalciuria, a normal or low serum level of 1,25-dihydroxyvitamin D (1,25(OH)²D), a normal serum level of parathyroid hormone (PTH), and increased activity of serum alkaline phosphatases. The phenotype is characterized by bone deformities and growth failure during childhood. With increasing age, many patients experience joint pain, bone fractures, and enthesopathy [2]. Both phosphate and activated vitamin D are usually required as treatment. It is necessary to guard against the exacerbation of the nephrocalcinosis (NC) and secondary or tertiary hyperparathyroidism (HPT) [3]. There are few reports of long-term complications in XLH other than skeletal and dental diseases. The aim of this study was to identify the phenotypic presentation of XLH during adulthood including complications besides skeletal and dental diseases. Additionally, we attempted a genotype-phenotype correlation analysis of the PHEX gene with regard to adult complications.
Materials and Methods

The analysis of long-term complications was performed in 22 patients with a PHEX mutation who attained final height, and were older than 18yr at the last visit. Among the 22 patients, 10 were male and 12 were female. The medical records of the patients treated in the past 30 years at the one institution, Tokyo Metropolitan Children’s Medical Center (formerly called Tokyo Metropolitan Kiyose Children’s Hospital), were systematically reviewed. Blood and urine samples were examined at least twice a year, and the dosage of phosphate and vitamin D were adjusted with the following aims: 1) 1.0 mg/dL or more increase of inorganic phosphorus (iP) from the basal to maximal serum level after oral administration of phosphate (maximal serum iP was usually obtained 60 minutes after oral phosphate intake). 2) Avoidance of hypercalciuria (urine calcium/creatinine over 0.3) and hypercalcemia (serum calcium level over 10.3 mg/dL). Renal ultrasonography was performed once in 2 years.

The disorders were defined as follows: hypertension: systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg; NC: generalized calcium deposition in the kidney visible by ultrasonography; renal dysfunction: serum cystatin C or serum creatinine value exceeding the reference value for each age and sex; secondary HPT: patients with high intact PTH levels (> 65 pg/mL) lasting over 6 months; tertiary HPT: patients necessitating a parathyroidectomy. We particularly examined hypertension with XLH. Patients were stratified according to age at the last visit, and the prevalence rate of hypertension between the XLH and age-matched control groups was compared. As the healthy control group, a survey of the Ministry of Health, Labour and Welfare was used [4]. The presence of clinical factors which could play a role in the pathogenesis of hypertension was studied. The patients were grouped into hypertension group and non-hypertension group, and analyzed correlation between hypertension and clinical parameters. Intact PTH was analyzed in limited patients with HPT. In patients with HPT, intact PTH value was used at the time of diagnosis of HPT. In non-onset of HPT patients, intact PTH value was used at last visit. Other clinical parameters were used at the value at last visit. Estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR (mL/min/1.73 m²) = 194 × Serum creatinine (-1.094) × Age (-0.287) × 0.739 (if female) [5].

We next examined the genotype-phenotype correlation of PHEX gene mutation. This analysis was performed only with males who were grouped by mutation type. 1 group was comprised of male patients with missense and in-frame mutations. The other group was comprised of those with any mutations which would result in truncated PHEX proteins. The following points were compared between these above two groups: the age of NC onset, dosage of phosphate and vitamin D at last visit, and Tmp/GFR value at age 7 years or older [6].

Statistical analysis was conducted using the chi-square test and unpaired t-test. The p value <0.05 was considered statistically significant. Data were analyzed using the Statistical Package for Social Sciences version 17.0 (SPSS, Chicago, Illinois).

This study was approved by the institutional review board of the Tokyo Metropolitan Children’s Medical Center (H25-76), and informed consent was obtained from either the participants or their parents.

Results

Most patients were treated with both phosphate and vitamin D (Alfacalcidol) from the time of diagnosis (Table 1). 1 patient (case 9) had been treated only with vitamin D during childhood. He started taking both phosphate and vitamin D at the age of 26 when his daughter was diagnosed with XLH. 2 patients had past history of treatment with growth hormone (case 4, case 8).

Six patients had hypertension, the average age of onset being 29.0 years. It was possible that the XLH patients had a higher rate of hypertension compared to the age-matched control groups (Fig. 1). In hypertensive patients, HPT preceded the development of hypertension except in 1 patient, who showed intact PTH for the first time at 21 years old (case 21). 1 patient developed tertiary HPT (case 13). 15 patients had NC. 2 patients had chronic renal dysfunction (case 20, case 21) (Table 1).

HPT and NC are suspected to be causes of hypertension. HPT and NC can be caused by the phosphate and vitamin D treatment for XLH. Therefore we also analyzed correlation between hypertension and weight-based dosage of phosphate and alfalcacidol, which were negative. Intact PTH, cystatin C, serum creatinine, eGFR, plasma renin activity, serum aldosterone, weight-based phosphate dosage and weight-based
Hypertension is a complication of XLH

### Table 1
Phenotype during adulthood

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<th>Age at last visit</th>
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<th>Age at NC diagnosis</th>
<th>Age at HT diagnosis</th>
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<th>Difference between FH and TH (cm)</th>
<th>Treatment interruption (age)</th>
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HPT, Hyperparathyroidism; NC, Nephrocalcinosis; HT, Hypertension; FH, Final height; TH, Target height; ND, No data.

### Fig. 1
Prevalence rate of hypertension

HR, Hypophosphatemic rickets.
alfaalcaldol dosage were shown in Table 2A. The difference in these clinical parameters between presence and absence of hypertension was compared as is Table 2B. Patients with hypertension had a significantly higher serum creatinine ($p=0.041$) and lower eGFR ($p=0.010$) compared to patients without hypertension. No correlation was found between cystatin C and hypertension. No significant difference was found in any other parameters.

Thirteen patients discontinued treatment (Table 1). During the treatment interruption, all male patients suffered bone fractures in their lower limbs, and 10 patients experienced lower back and leg pain. Pain improved in all of the patients after recommencement of phosphate and vitamin D therapy. All patients had a lower final height than the target value. The average value of the difference between the target and final height in sporadic male and female were -15.4 cm

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<th>NC</th>
<th>HT</th>
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<th>Serum cystatin C (mg/L)</th>
<th>Serum creatinine (mg/dL)</th>
<th>eGFR (mL/min/1.73m²)</th>
<th>Plasma renin activity (ng/mL/hr)</th>
<th>Serum aldosterone (pg/mL)</th>
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<td>0.86</td>
<td>0.83</td>
<td>81.9</td>
<td>0.8</td>
<td>58.8</td>
<td>20</td>
<td>0.034</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>42</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>74</td>
<td>1.52</td>
<td>1.37</td>
<td>34.8</td>
<td>9.5</td>
<td>201</td>
<td>14</td>
<td>0.031</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>49</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>80.2</td>
<td>1.18</td>
<td>1.07</td>
<td>43.6</td>
<td>0.5</td>
<td>78.5</td>
<td>0</td>
<td>0.029</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>65</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0.50</td>
<td>92.4</td>
<td>ND</td>
<td>ND</td>
<td>9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HPT, Hyperparathyroidism; NC, Nephrocalcinosis; HT, Hypertension; eGFR, Estimated glomerular filtrating ratio; ND, No data.

Renin and aldosteron were measured in the decubitus position.
Serum cystatin C : Reference value : M 0.65-0.95, F 0.56-0.87
Serum creatinine : Reference value : M 0.61-1.04, F 0.47-0.79

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intact PTH</th>
<th>Serum cystatin C</th>
<th>Serum creatinine</th>
<th>eGFR</th>
<th>Plasma renin activity</th>
<th>Serum aldosterone</th>
<th>Phosphate dosage</th>
<th>Alfacalcidol dosage</th>
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<tbody>
<tr>
<td>$p$-value</td>
<td>0.458</td>
<td>0.145</td>
<td>0.041</td>
<td>0.010</td>
<td>0.132</td>
<td>0.411</td>
<td>0.241</td>
<td>0.756</td>
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</tbody>
</table>
Hypertension is a complication of XLH. In this study, the phenotype 22 patients, including their blood pressure and well-known complications [2, 7], were examined. We showed that XLH patients can develop hypertension at a relatively young age. Only 1 study has been reported by Alon US *et al.* describing hypertension as a complication of XLH [8]. This study further supported the view that hypertension could be one of the characteristic symptoms of XLH in adulthood.

The genotype-phenotype correlation analysis was performed in 10 adult male patients as described (Table 3A, 3B): age of NC onset: \( p = 0.063 \); dosage of phosphate: \( p = 0.771 \); dosage of vitamin D: \( p = 0.600 \); Tmp/GFR value: \( p = 0.168 \). The age at NC onset was younger in the non-missense mutation group than in the missense mutation group (Fig. 2), although this difference was not significant.

### Table 3A Genotype and phenotype in adult males

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Case</th>
<th>Tmp/GFR</th>
<th>Phosphate dosage (mg/kg/day) at last visit</th>
<th>Alfacalcidol dosage (μg/kg/day) at last visit</th>
<th>Age at NC diagnosis</th>
<th>Age at last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splice site 2</td>
<td>2</td>
<td>1.3</td>
<td>8.5</td>
<td>0.043</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Splice site 4</td>
<td>4</td>
<td>1.6</td>
<td>18.6</td>
<td>0.031</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Splice site 11</td>
<td>11</td>
<td>1.5</td>
<td>0</td>
<td>0.034</td>
<td>ND</td>
<td>30</td>
</tr>
<tr>
<td>Nonsense 1</td>
<td>1</td>
<td>1.6</td>
<td>7.3</td>
<td>0.036</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Nonsense 5</td>
<td>5</td>
<td>1.4</td>
<td>10.2</td>
<td>0.034</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Frame shift</td>
<td>8</td>
<td>1.2</td>
<td>18.4</td>
<td>0.04</td>
<td>BO</td>
<td>24</td>
</tr>
<tr>
<td>Missense 9</td>
<td>9</td>
<td>1.5</td>
<td>27.8</td>
<td>0.042</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Missense 14</td>
<td>14</td>
<td>1.8</td>
<td>ND</td>
<td>ND</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Missense 17</td>
<td>17</td>
<td>2.2</td>
<td>11</td>
<td>0.038</td>
<td>BO</td>
<td>39</td>
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<tr>
<td>Missense 19</td>
<td>19</td>
<td>1.3</td>
<td>10.2</td>
<td>0.034</td>
<td>36</td>
<td>41</td>
</tr>
</tbody>
</table>

ND, No data; BO, Before onset; NC, Nephrocalcinosis.

### Table 3B Correlation between genotype and phenotype

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tmp/GFR</th>
<th>Phosphate dosage (mg/kg/day) at last visit</th>
<th>Alfacalcidol dosage (μg/kg/day) at last visit</th>
<th>Age at NC diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p )-value</td>
<td>0.168</td>
<td>0.771</td>
<td>0.6</td>
<td>0.063</td>
</tr>
<tr>
<td>Average value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-missense mutation group</td>
<td>1.4</td>
<td>10.5</td>
<td>0.036</td>
<td>10.8</td>
</tr>
<tr>
<td>Missense mutation group</td>
<td>1.7</td>
<td>16.3</td>
<td>0.038</td>
<td>27.3</td>
</tr>
</tbody>
</table>

NC, Nephrocalcinosis.

**Fig. 2** The age at NC onset in the non-missense mutation group and the missense mutation group.
It remains to be established what factors could cause hypertension in this disorder. Chronic renal dysfunction and HPT are suspected to be causes of hypertension. First, the association between primary HPT and hypertension has been accepted, with the prevalence of the latter varying between 20 and 80% [9]. Activation of the renin-angiotensin-aldosterone system by PTH is regarded as one of the reasons that PTH may lead to hypertension. In this study, either the plasma renin or aldosterone in 3 patients with both HPT and hypertension were high (case 6, case 18, and case 20). However, no correlation was found between intact PTH, plasma renin activity, serum aldosterone and hypertension. Secondly, NC is another possible cause of hypertension by inducing renal dysfunction and renal vascular hypertensive [8]. In this study, patients with hypertension had a significantly higher serum creatinine and lower eGFR. However, it was possible that the results were influenced by other factors such as age. For this reason, renal dysfunction was not able to be considered the only cause of hypertension. Multiple factors such as renal dysfunction, HPT and age presumably play a role in the development of hypertension. Considering the limited number of our patients, further study is clearly necessary to address a potential cause of hypertension. The patients with HPT or NC must be monitored carefully to guard against the development of hypertension.

As far as limitation of this study is concerned, this study did not adjustment for factors other than age, such as smoking, obesity, sodium intake, or other genetic factors. These other parameters may have influenced the results.

We also attempted a genotype-phenotype correlation analysis of PHEX phenotypes in adults. While some previous studies have examined the genotype-phenotype correlation in terms of skeletal disease and laboratory findings at the time of diagnosis [3, 10-12], few studies have reported on long-term complications other than skeletal and dental disease. Female patients could have phenotypic heterogeneity due to skewed X chromosome inactivation. Therefore, we analyzed only male patients, and confirmed that there was no significant relationship between the phenotype and genotype in the age of NC onset, dosage of phosphate and vitamin D during adulthood, or Tmp/GFR value. The current therapy for XLH is not ideal. Secondary HPT, renal dysfunction, and NC are suspected to be potential side effects of long-term administration of high-doses of phosphate and vitamin D. Dose of phosphate and vitamin D should be tightly regulated. However, insufficient treatment can in turn lead to complications such as bone fractures, which impact quality of life [2]. Recently, however, a new therapy using anti-FGF23 antibody has been tested [13, 14], and hexa-D-arginine was also reported as a new therapeutic agent [15], holding out the hope of the development of new methods of treatment with fewer complications.

In conclusion, the results of this study supported the hypothesis that early-onset hypertension may be one of the characteristic complications of XLH, and underscored the need for careful lifelong treatment of XLH patients. It remains to be elucidated whether these early onset hypertension is primarily due to XLH or secondarily due to the treatment / complication. Further studies are necessary to confirm these results.

Acknowledgments

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References

Hypertension is a complication of XLH.


