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X-Linked Hypophosphatemic Rickets: Case Report

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SUMMARY

Introduction X-linked hypophosphatemic rickets (XLHR) is a dominant inherited disease caused by isolated renal phosphate wasting and impairment of vitamin D activation. We present a girl with X-linked hypophosphatemic rickets (XLHR) as a consequence of de novo mutation in the PHEX gene.

Case Outline A 2.2-year-old girl presented with prominent lower limb rachitic deformity, waddling gait and disproportionate short stature (79 cm, <P5; -1,85 SD). On the basis of hypophosphatemia, hyperphosphaturia, high serum level of alkaline phosphatase, normal calcemia, 25(OH)D and PTH, as well as characteristic clinical and X-ray findings, diagnosis of hypophosphatemic rickets (HR) was made. Normal calciuria and absence of other renal tubular disorders indicated HR as a consequence of isolated hyperphosphaturia. The treatment (phosphate 55 mg/kg and calcitriol 35 ng/kg per day), introduced 15 month ago, resulted in a stable normalization of alkaline phosphatase and phosphorus serum levels (with intact calcemia and calciuria), disappearance of X-ray signs of the active rickets and improvement of the child's longitudinal growth (0.6 cm per month). Subsequently, by detection of already known mutation in the PHEX gene: c.1735G>A (p.G579R) (exon 17), XLHR was diagnosed. Analysis of the parental PHEX gene did not show the abnormality, which indicated that the child's XLHR was caused by *de novo* mutation of this gene.

Conclusion Identification of genetic defects is exceptionally significant for diagnosis and differential diagnosis of hereditary HR.

Keywords: X-linked hypophosphatemic rickets; diagnostics; therapy

INTRODUCTION

Rickets, i.e. osteomalacia during the period of growth and development represents a highly heterogeneous clinical entity, both from the aspect of etiopathogenesis and clinical expression, therapy and prognosis [1, 2]. It results from the negative calcium and/or phosphorus balance, most often due to vitamin D deficiency, and exceptionally rare due to its activation disorder, deficiency of receptor $1,25(OH)_2$, and calcium and phosphorus deficit caused by their insufficient intake or pathological loss through the urine [1-4]. Accordingly, it is classified into two basic forms: calcium deficit and phosphorus deficit [2, 5]. Although from the pathogenic viewpoint such systematization of rickets seems clear enough, it should be pointed out that, due to close association of calcium and phosphorus metabolism, it is not absolutely divisible [2, 3]. The result of this occurrence, i.e. the secondary deficit of phosphorus in the lack of calcium or vice versa, is the participation, not only of parathyroid hormone (PTH) and $1,25(OH)_2$, but also of other mediators responsible for their homeostasis [3, 6, 7]. This primarily refers to phosphatonins, fibroblast growth factor 23 (FGF-23) and other, which, in synchronous activity with aforementioned factors, provide the entire body homeostasis of phosphorus and calcium [8-11]. Hence, different pathological conditions, either at the level of regulatory or effector systems, cause the deficit of these two macroelements with osteomalacia as predominant manifestation [9, 10, 11]. The spectrum of such diseases, both hereditary and acquired, is highly extensive. One of them is X-linked hypophosphatemic rickets (XLHR) which we present on the example of our patient whose diagnosis has been also confirmed genetically.

CASE REPORT

A 2.2-year-old girl presented with typical rachitic deformities, predominantly manifested in the bones of the lower extremity (coxa vara and genu varum), waddling gait and disproportionately short stature (body height 79 cm, <P5; -1.85 SD) (Figure 1). She was born from normal term pregnancy as a first of two children from healthy parents with body weight of 3100 g, body length of 51 cm and head circumference of 34 cm. Through the first year, along with breastfeeding during the first six months followed by standard cow's milk dietary, the patient was on regular intake of 667 IU of vitamin D. She sprouted her first teeth at 7 months, and started to walk at 12 months when first aforementioned skeletal deformities were manifested. As her mother's father had somewhat lower stature and genu varum, the child's problem was attributed to harmless inherited disorder, so that during the following 14 months she was under orthopedic follow-up. On the basis of characteristic history

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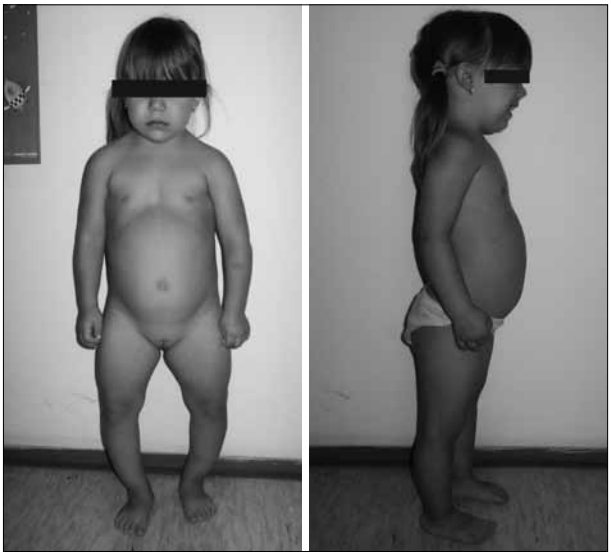

Figure 1. Our patient with XLHR

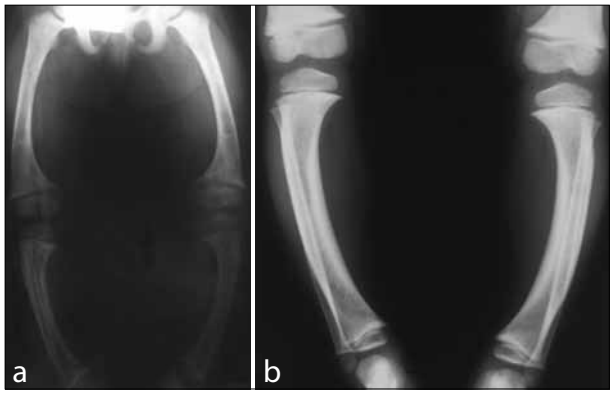

Figure 2. X-ray of the lower extremities in our patient with XLHR at diagnosis (a) and after 11 months of treatment (b)

data and clinical and X-ray picture, as well as the findings of hypophosphatemia (0.84 and 0.9 mmol/L), increased phosphorus creatinine ratio (mg/mg) in 24-hour urine (5.63), hyperphosphatasemia (547 U/L, normal <383 U/L) and adequate serum level of calcium (2.47 and 2.62 mmol/L), 25 (OH)D (40,6 ng/ml) and PTH (40 pg/ml), the diagnosis of hypophosphatemic rickets (HR) was made. Normal calcium/creatinine ratio (mg/mg) in 24-hour collection of urine (0.25) and absence of other disorders of tubular function indicated HR with an isolated hyperphosphaturia. After the confirmed diagnosis a therapy was initiated (phosphate 55 mg/kg/day in six divided doses and calcitriol 35 ng/kg/day in two doses); it resulted in stable normalization of alkaline phosphatase and phosphorus serum levels, with the intact calcemia and calciuria, disappearance of X-ray signs of the active rickets (Figure 2) and satisfactory longitudinal growth velocity of the child (0.6 cm per month). Up-to-now, there have been no evident signs of deformity correction of the lower extremities. Over the last 15 months of follow-up, neither signs of nephrocalcinosis nor any other adverse effects of treatment were recorded. At the latest control, after 11 months of treatment, calcium/creatinine (mg/dl) ratio was 0.35, so that, beside the advice for better diuresis, daily dosage of Calcitriol was decreased to 23.5 ng/kg.

Subsequently, XLHR was identified by detection of already known mutation in the PHEX gene: c.1735G>A (p.G579R) (exon 17). Maternal and paternal analysis of PHEX did not show any abnormality which indicated that the child's XLHR developed as the result of *de novo* mutation of this gene. Mother gave birth to another child, now 18-month old girl, who is healthy.

DISCUSSION

XLHR is a dominant inherited disease caused by isolated renal phosphate wasting and impairment of vitamin D activation [1, 15, 16, 17]. It is the most common form of heritable rickets, with incidence of 1:20,000 live births [1, 12]. The basis of XLHR is the inactivating mutations in the PHEX gene (phosphate regulating gene with homologies to endopeptidases on the X chromosome) which is located in Xp22.1-22.2 [13-18].

The PHEX gene is expressed in bone, teeth and parathyroid glands and, by yet unexplained mechanisms, negatively regulates FGF-23 expression [6, 10, 13]. The FGF-23, the product of gene located on the chromosome 12p13, is a bone protein hormone with phosphaturic effect directed to maintain circulating phosphate levels within a normal range [10-13, 18-20]. It is excreted by osteocytes and osteoblasts as the physiological response to hyperphosphatemia [6-11, 21]. The same effect on the expression of the FGF-23 has elevated $1,25(OH)_2D$ level in the blood and probably PTH [6, 10]. The FGF-23, in synergistic activity with PTH, increases renal inorganic phosphate excretion by inhibiting the expression of renal sodium-phosphate cotransporters NaPi-IIa and NaPi-IIc in the proximal tubules [6, 13]. The FGF-23 also suppresses 25(OH)D 1-α hydroxylase (P450c1α) and conversely enhances the expression of CYP24A1 (24-hydroxylase) activity in the mitochondria of the proximal renal tubule leading to reduced circulating levels of $1,25(OH)_2D_3$ and consequently to decreased intestinal resorption and tubular reabsorption of phosphorus [6, 13, 22-25]. Additionally, the deficit of $1,25(OH)_2D$ also decreases the intestinal absorption of calcium, as well as its proximal tubular reabsorption [8, 22, 23].

Aforementioned facts indicate that the FGF-23 is, as a part of hormonal bone-parathyroid-kidney axis, the essential participant in the regulation of the homeostasis of phosphorus, and partially of calcium, thus also of the bone system, as well as that its dysregulation, either in the sense of excess or deficit can basically disturb this homeostasis [6, 7]. There are numerous diseases, hereditary and acquired, which occur as the result of increased or decreased activity of the FGF-23 [11, 25-29]. One of them, caused by inactivating mutations in the PHEX gene and the consequent excess of FGF-23 followed by isolated renal phosphate wasting and rickets, is XLHR [1, 16, 25]. Beside XLHR, in the group of hereditary HR with isolated renal phosphate wasting, there are three autosomal forms with a much lesser incidence and similar clinical presentation [1, 2]. These include autosomal dominant HR, caused by

mutations in the FGF-23 gene and autosomal recessive HR caused by mutations in dentin matrix protein 1 gene and mutations in ectonucleotide pyrophosphatase/phosphodiesterase-1 gene [26, 27]. In addition, in rare cases HR may be caused by tumor hypersecretion of FGF-23 [28, 29].

Our patient is a classic example of XLHR, both from the clinical and genetic aspect. The disease occurred as the consequence of de novo already known mutation in the PHEX gene c.1735G>A (p.G579R) (exon 17). This refers to one of over 250 so far described mutations [13]. The initial diagnosis was clinical, because our institution lacked the facilities for its genetic verification. Treatment result is outstanding and there have been no adverse effects until now. During the last 15 months the patient has grown 9 cm (0.6 cm per month), which is satisfactory for her age and gender. X-ray signs of the active rickets have disappeared; nevertheless, until these days, there has been no evident improvement of deformities of the lower extremities.

In conclusion, HR caused by isolated renal phosphate wasting involves a heterogeneous group of hereditary and acquired diseases with similar clinical presentation. All of them occur as the consequence of FGF-23 hypersecretion. The classical diagnostic approach enables the diagnosis of this form of rickets, but not the precise differentiation of its entities. However, as can be seen on the example of our patient, genetic analysis provides not only a reliable verification of XLHR as a variant of HR, but also the insight into the type and origin of mutation.

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X-везани хипофосфатемијски рахитис – приказ болесника

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КРАТАК САДРЖАЈ

Увод *X*-везани хипофосфатемијски рахитис је доминантна наследна болест узрокована изолованим реналним губитком фосфора и смањеном активацијом витамина Д. Приказујемо девојчицу с овим обољењем као последицом мутације гена *PHEX de novo*.

Приказ болесника Девојчица узраста од 2,2 године доведена је код лекара због рахитисних деформитета предоминантно испољених на доњим екстремитетима, гегавог ходања и непропорционално ниског раста (79 *cm*, *<P5*; -1,85 *SD*). На основу хипофосфатемије, хиперфосфатурије, високог нивоа алкалне фосфатазе у серуму, нормалне калцемије, вредности *25(OH)D* и *PTH*, као и типичног клиничког и рендгенског налаза, постављена је дијагноза хипофосфатемијског рахитиса (ХР). Нормална калциурија и изостанак других поремећаја тубула бубрега указивали су на ХР као последицу изоловане хиперфосфатурије. Одговарајућа петнаестомесечна терапија (фосфор у дози од 55 *mg/kg* и калцитриол у дози од 35 *ng/kg* дневно) довела је до стабилне нормализације нивоа алкалне фосфатазе и фосфора у серуму (уз непромењену калцемију и калциурију), ишчезавања рендгенских знакова активног рахитиса и побољшања лонгитудиналног раста детета (0,6 *cm* месечно). Накнадно је, откривањем познате мутације у гену *PHEX*, *c.1735G>A (p.G579R) (exon 17)*, установљен *X*-везани ХР. Анализа *PHEX* гена родитеља није показала абнормалност, што указује на то да је обољење код детета узроковано мутацијом овог гена *de novo*.

Закључак Утврђивање генског оштећења је веома значајно у дијагностиковању и диференцијалној дијагностици наследног ХР.

Кључне речи: *X*-везани хипофосфатемијски рахитис; дијагностика; лечење

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