Growth hormone treatment of 2 patients with X-linked hypophosphatemic rickets caused by PHEX mutation: effects on linear growth

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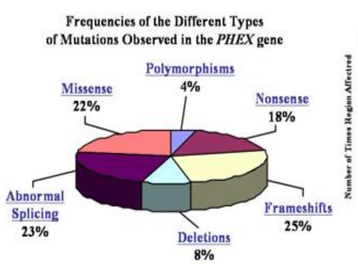
OBJECTIVES

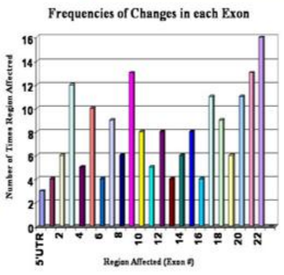
Hypophosphatemic rickets (HR) is a group of rare disorders caused by an excessive renal phosphate wasting. X-linked HR (XLHR) is caused by mutation in *PHEX* (phosphate-regulating endopeptidase) gene and is characterized mainly by bone deformities, disproportionately short stature, dental anomalies and hypophosphatemia with coexisting low renal phosphate reabsorption. Early treatment with vitamin D and phosphate improves the patient's growth. Recombinant human growth hormone (rhGH) may also improve growth in XLHR through a direct effect on growth cartilage, and by increasing renal phosphate reabsorption and serum phosphate levels.

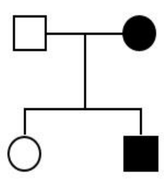
X-Linked Dominant Hypophosphatemic Rickets

PHEX Endopeptidase
Xp22.1
22 small exons (17 less than 130bp)

193 mutations reported (www.phexdb.mcgill.ca)







AIM OF STUDY

The aim of the study was to investigate the clinical phenotype and molecular background of HR in a family in which XLHR was suspected.

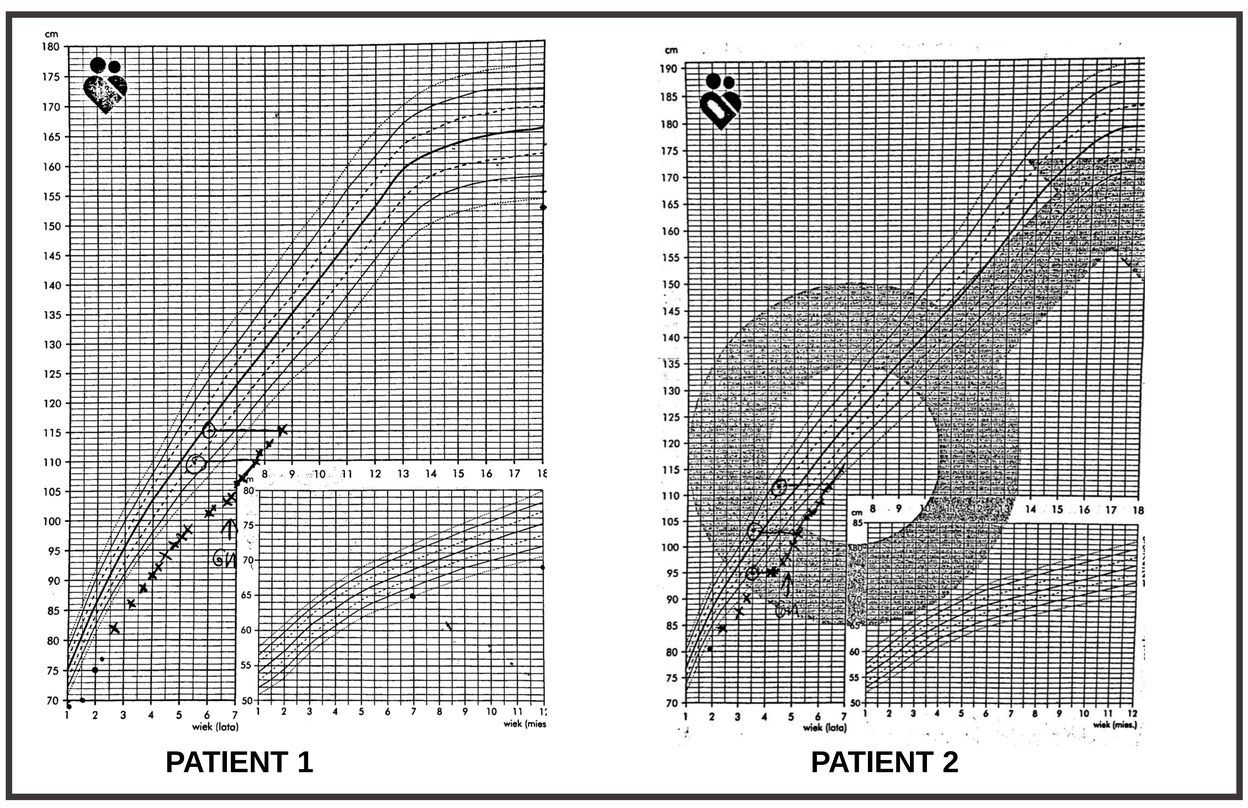
CASE PRESENTATION

2 patients, 8.25 years old girl and 6.75 years old boy were diagnosed with HR at the age of 2.25 years and then treated with alfacalcidol (73 and 69 ng/kg/d) and phosphorus (175 and 30 mg/kg/d). Due to the diagnosis of growth hormone deficiency rhGH therapy was initiated at the age of 6.75 years and 4.75 years, respectively (current doses of rhGH are 0,029 and 0.028 mg/kg/d).

Patient	Sex	Age	Age at diagnosis	Ht SDS at diagnosis/1st stay at department	Current Ht SDS	Clinical symptoms/ family interview	Ear problems	Dental problems	Other clinical features	Max GH After stimulation Normal range > 10 ng/ml	Current treatment
1	F	8 3/12	2 3/12	-3,7	-3.4	bowing of lower limbs, short stature **AFFECTED FATHER**	no	no	no	5.2	rhGH: 0.029 mg/kg/d Phosphorus: 175 mg/kg/d Alfacalcidol 73 ng/kg/d
2	M	6 9/12	2 3/12	-2.3	-2.1	bowing of lower limbs, short stature, frontal bossing, widening of distal parts of forearms	no	gingivitis	no	7.1	rhGH: 0.028 mg/kg/d Phosphorus: 30 mg/kg/d Alfacalcidol 69 ng/kg/d

PATIENT	S-Ca (N 2,2-2,7 mmol/l)	S-P (N 4-7 mg/dl)	S-ALP (N 93-309 IU/L)	S-PTH (N 15-68,3 pg/ml)	S-25(OH)D3 (N 9,4-59,1; opt. 30-50 ng/ml)	U-Ca (N <4 mg/kg/d)	U-P (N16-20 mg/kg/d)	TRP1 % (N>80%) At the diagnosis	TRP2 % (N>80%) During therapy
1	2,44	**↓3,13**	**↑ 522**	**↑354**	21	39,6	0,4	**↑ 23,28**	84
2	2,59	**↓2,46**	**↑ 730**	**↑335**	30,7	26,4	0,2	**↑ 42,1**	84

S – serum U – urine ALP – alkaline phosphatase TRP - Tubular reabsorption of phosphate



PATIENT 1 **PATIENT 2**

METHODS AND RESULTS

DNA was isolated from fresh blood and all exons of *PHEX* gene were amplified using PCR and directly sequenced.

The dominant clinical signs in both patients were bowing of legs and short stature. HtSDS at the time of diagnosis was -3.7 and -2.3, respectively. Current htSDS is -3.4 and -2.1, respectively and the height gain during rhGH therapy was +0.3 and +1.04 SD. **In the patient 1, we found a known c.C716>T, p.T239M heterozygous polymorphism (rs7955866) in *FGF23* gene which was absent in the patient's affected father. We also found a novel heterozygous mutation c.326_327insCA, N110Ifs*7 in *PHEX* gene which was also present in the patient's father. *FGF23* in the patient 2 was intact, but we found a known hemizygous mutation c.1801_2250del in *PHEX* gene covering exon 17 to exon 22.**

CONCLUSIONS

- Early clinical and molecular diagnosis of HR, and early implementation of vitamin D and phosphorus is crucial to prevent severe bone deformities and to improve final height.
- rhGH therapy in patients with XHLR may be very effective in those with coexisting growth hormone deficiency.
- Genetic counseling in families with HR patients should be proposed.

References

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