Clinical phenotype and molecular studies in patients with hypophosphatemic rickets

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BACKGROUND

Hypophosphatemic rickets (HR) is a group of rare disorders caused by excessive renal phosphate wasting. The dominant form of HR is X-linked HR (XLHR) caused by mutation in the phosphate-regulating endopeptidase gene *PHEX*. There is also autosomal dominant form of HR caused by mutation in *FGF23* gene or rare autosomal recessive form caused by *DMP1* mutation. The phenotype can vary from very delicate to severe bone disease.

The aim of the study was to investigate the clinical and molecular background of HR in 5 patients.

Patients and Methods: 5 patients aged 2-8 years (2 girls and 3 boys) diagnosed with HR due to clinical and biochemical picture.
In each of these patients three exons of the *FGF23* gene were directly sequenced after polymerase chain reaction amplification of the entire coding region. Additionally, in one patient *PHEX* gene was also analyzed by direct sequencing (in the four remaining the analyses are ongoing).

RESULTS

1. Bowing of legs was the dominant symptom in all patients.
2. All patients presented hypophosphatemia, increased alkaline phosphatase concentration with normal levels of serum calcium and 25OHD3. In all children with the time the increased loss of phosphorus with urine and decrease of tubular reabsorption of phosphate (TRP) was observed.
3. In one patient analysis of the *FGF23* gene revealed the presence of one polymorphism c.C716>T, p.T239M. The remaining four patients were *FGF23* mutation-negative. In one patient the already known *PHEX* gene deletion was found encompassing exons 17-22.

Fig 1. The characteristic bowing of legs of one of the patients.

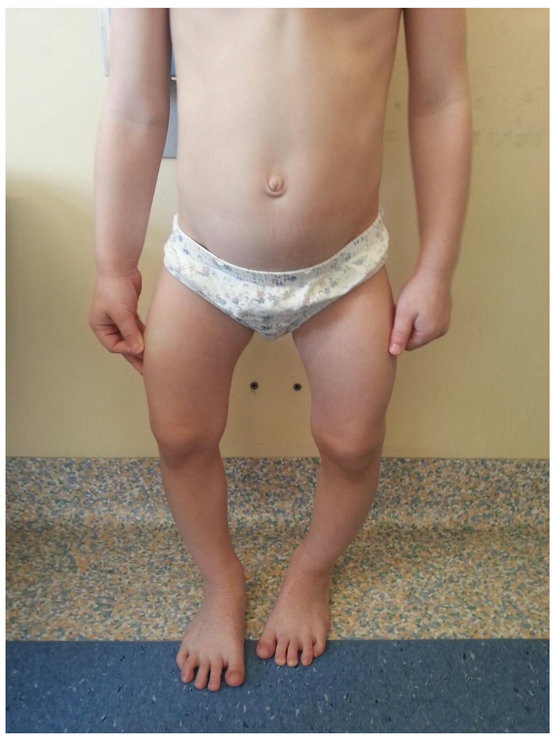

Table 1. Chosen parametres in the studied group.

Patient's number	Age at diagnosis	Sex	Long bone deformities	Dental/ peridental problems	Other clinical problems	S-Ca	S-P	S-ALP	S-PTH	S-25(OH)D3	U-Ca	U-P	TRP 1	TRP 2	PHEX	FGF23
	yrs/months	M/F				mg/dl	mg/dl	U/L	pg/ml	ng/ml	mg/kg/d	mg/kg/d	%	%	Pos/Neg	Pos/Neg
1	2 3/12	F	bowing of lower limbs, short stature	no	no	9.76	3.13	522	21	39.6	0.4	23.28	84	69	not tested	polymorphism c.C>716T p.T239M in exon 3
2	7	F	bowing of lower limbs, short stature, lumbar hyperlordosis.	no	no	10.2	2.89	407	11.5	22.8	3.6	21.3	96	71	not tested	negative
3	2 3/12	M	bowing of lower limbs, short stature, frontal bossing, widening of distal parts of forearms	yes	no	10.36	2.46	730	30.7	26.4	0.2	42.1	84	68	deletion of exons 17-22	negative
4	2 8/12	M	bowing of lower limbs, short stature.	yes	immunodeficiency, (hypogammaglobulinemia)	10.48	2.57	723	36.6	37.6	0.85	21.35	91	72	not tested	negative
5	1 1/12	M	bowing of lower limbs, short stature, widening of distal parts of forearms	no	immunodeficiency suspected	10.28	2.52	1079	64.2	79.1	1.4	26.7	78	71	not tested	negative

CONCLUSIONS

1. **The early diagnosis of HR is very important for proper treatment and to prevent bone deformities.**

2. **The molecular analysis of *FGF23* and *PHEX* gene is very important for the confirmation of clinical diagnosis of hypophosphatemic rickets and highlights the role of further genetic counselling in families with HR patients.**