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HYPOPHOSPHATEMIC RICKETS: ENPP1 mutation case report

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Introduction

Although vitamin D deficit is the most common cause of rickets there are many rare genetically transmitted forms as hypophosphatemic rickets, a family of hereditary diseases characterized by low phosphorous plasma levels and resistance to 25OH-vitamin D replacement.

Case report

3.6 year-old Italian child was sent from the General Pediatrician for rickets suspicion. Silent personal history and familiar anamnesis, no history of consanguinity. Breast-fed until 11 month-old and regularly supplementation with 25OH-vitamin-D for 12 months after birth.

Examination:
- 94.3 cm (25° centile, -1.25 SDS) ; 14.5 kg (25° centile, -0.69 SDS); TH 172 cm (75° centile).
- Clinical features: rachitic rosary, bracelet and femoral bowing.
- Biochemical data (see Table 1).
- X ray lower limbs: bowing of femur with enlargement and structural irregularities of distal metaphyseal epiphyseal regions; similar features also present at the tibia level.

Diagnosis: clinical and radiological data were compatible with the diagnosis of rickets. Normocalcemia and normal levels of 25(OH)D after three months of 25OH-vitamin D supplementation), combined with normal PTH values, in presence of hypophosphatemia, suggested vitamin D resistant hypophosphatemic rickets.

Genetic investigations positive for two variants in heterozygous in the ENPP1 locus: c.715+2T>g translocation in exon's 6 splicing site and c.1437+3_1437+6del4 deletion in intron 14 (ARHR2), responsible for a rare autosomal-recessive form of the disease. The same mutations have been confirmed respectively in mother and father (healthy genetic carriers).

Follow-up: 2/6 systolic pulse with a pathological echocardiogram showing calcification at the aortic valve. Reduced growth velocity, bilateral transmitting hypoacusia, lower limbs pain, fatigue and dental enamel disturbances.

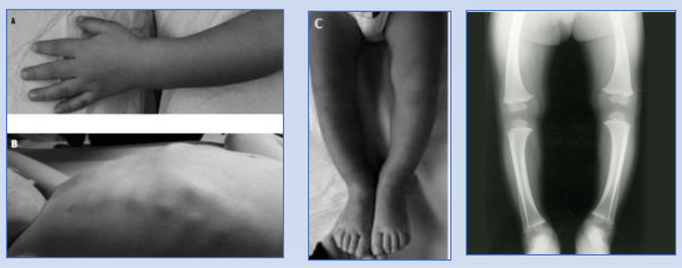
Treatment : active vitamin D metabolite, 1,25(OH)2D pills 250 ng: start dose 17.2 ng/kg/day; associated with inorganic phosphorous salts pills 195.6 mg: start dose 26.9 ng/kg/day divided in 3 poses/day (see Table 2)

Table 1.

Age	3.6	4.10	5.9	6.8	7.9	9.2	y
Ca	2.2	2.12	2.45	2.36	2.37	2.48	mmol/l (2-2.6)
P	0.84	0.74	0.75	0.78	0.86	0.82	mmol/l (1.1-1.94)
ALP	527	506	592	605	555	527	UI/l (150-380)
PTH	52.7	71.1	26.9	27	34	30	pg/ml (1-84)
25(OH)D	20	26	31.5	41.3	36	31.3	>30 ng/ml
Creatinine	0.26	0.29	0.35	0.34	0.38	-	mg/dl
uCa/uCr	0.06	0.04	0.03	0.15	0.16	0.13	mg/mg (< 0.35)
Tubular reabsorption of phosphate (TRP)	82	69.5	73.1	67	69	-	% (70-100)
Clinical Manifestations	- rachitic rosary , bracelet and femoral bowing	- tibialis deformity and varus foot - 2/6 systolic pulse	- wrist, knee, ankle pain and fatigue	- pain in thigh addution, difficulty to run	-transmitting hypoacusia - dermatitis		
Orthopedic visit	No indications to surgery	-	-	-	-	right distal femoral emiepiphisiolesi surgery	
Growth velocity	7.2 cm/y	9.1 cm/y	8 cm/y	9.4 cm/y	5.3 cm/y	5.5 cm/y	

Table 2.

Patient's age	3 y 7/12	3 y 10/12	4 y 11/12	6 y 4/12	7 y 0/12	7 y 5/12	7 y 9/12	9 y 2/12
Active vitamin D metabolite 1,25(OH)2D pills 250 ng: ng/kg/day	17	16	27	20	19	18	17	29
Inorganic phosphorous salts pills 195.6 mg: mg/kg/day	26.9	32.6	31.7	28.5	30	29	34.9	34.5



Discussion

With current therapy based on supplementation of phosphate and 1,25(OH)2D complete healing of the osteomalacia and correction of the biochemical abnormalities are generally incomplete, especially in ENPP1 patients, because we have to balance phosphorus levels with risk of calcifications.. The advances in our understanding in the pathogenesis of this mutation lead to new therapeutic strategies as like Na-Pyrophosphate, but further studies are needed to find new prospects for the management of the disease.
Patients affected by hypophosphatemic rickets need to start a multidisciplinary follow-up including endocrinologist, orthopaedic, odontoiatric and cardiologist specialists.

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