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Hylonome

Clinical Quiz

Hip fracture leading to the diagnosis of autosomal dominant hypophosphatemic rickets. A case report

S. Tournis[1], T. Koromila[2], N. Chatzistamatas[3], M. Droggaris[3], C. Zafeiris[1], K. Makris[4], H. Marketou[4], N. Papaioannou[1], P. Kollia[2], S. Gazi[3]

[1]Laboratory for Research of Musculoskeletal System "Theodoros Garofalidis", University of Athens, KAT Hospital, Athens, Greece; [2]Department of Biology, Laboratory of Human Genetics, University of Athens, Athens, Greece; [3]Rheumatology Department, KAT Hospital, Athens, Greece; [4]Biochemistry Department, KAT Hospital, Athens, Greece

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Case

A 38 year-old Caucasian female (weight: 67 Kg, height: 163 cm) was referred to our department after surgical treatment of a non-healing hip fracture, due to severe hypophosphatemia. During the previous ten months she suffered from worsening generalized bone pain, especially at the left hip, and proximal muscle weakness. There was no history of trauma. Past history revealed two distinct episodes of diffuse musculoskeletal pain following her pregnacies at 28 and 34 years respectively, that resolved spontaneously after three months. Family history was negative, and her two children (ten and six-years old males, respectively) had normal phosphate levels (4.6 mg/dl and 4.3 mg/dl, childrens normal range: 3.6-5.8 mg/dl). On clinical examination there were no lower extremity deformities. Radiology investigation (Figure 1A) revealed a transcervical fracture of the left femur with delayed union and varus deformity, looser zones on pubic rami and right *ischial ramus* and diffuse osteopenia with biconcave deformation of lumbar vertebrae. Bone mineral density at the right hip was quite below the expected range for age (FN: 0.556 mg/cm^2, Z-score: -3.8). Laboratory investigation revealed severe hypophosphatemia (1.7 mg/dl), phosphaturia (TMP/GFR: 1.4 mg/dl), normal calcium, iPTH and 25(OH) D levels, elevated total and bone specific alkaline phosphatase, while calcitriol levels were inappropriately normal (Table 1). Urinary amino-acid excretion was nor-

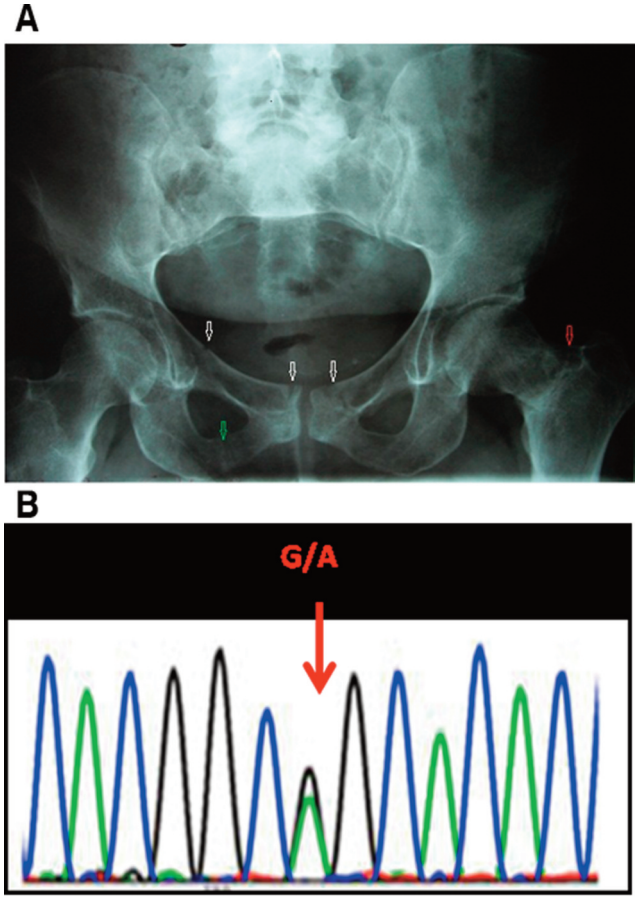

Figure 1. (**A**) Hip and pelvis radiograph: Transcervical fracture of the left femur with delayed union (red arrow) and varus deformity. Looser's zones on pubic rami *(white arrows)* and on the right ischial *ramus (green arrow)*. (**B**) Sequence chromatogram covering the detected p.R176Q mutation identified in ADHR patient amplified from genomic DNA (QIAamp DNA Blood Mini Kit (QIAGEN). Genomic DNA wild - type sequences were obtained from GenBank. The red arrow indicates the 527G>A (arginine to glutamine) mutation's site detected.

The authors have no conflict of interest.

Corresponding author: Symeon Tournis M.D., PhD., Laboratory for Research of the Musculoskeletal System "Th. Garofalidis", University of Athens, KAT Hospital, 10 Athinas Str., Kifissia, PC: 14561, Athens, Greece
E-mail: stournis@med.uoa.gr

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	Baseline	1 year	Normal limits
Ca (mg/dl)	9.0	9.4	8.2-10.2
P (mg/dl)	1.7	2.4	2.7-4.5
Creatinine (mg/dl)	0.6	0.61	0.5-1.1
iPTH (pg/ml)	41.0	29.0	10-65
25(OH)D (ng/ml)	28.5	24.2	20-58
$1,25(OH)_2$(pg/ml)	20.4	-	16-42
Alkaline Phosphatase (IU/L)	141.0	87.0	40-104
BSAP (ng/ml)	51.6	17.8	5.8-14.8
CaU24h (mg)	40.96	121.2	100-300
PU24h (mg)	750.0	574.0	400-1300
TMP/GFR (mg/dl)	1.4	2.3	2.5-4.2
Ferritin (ng/ml)	17.04		15-200
BMD FN (mg/cm^2/z-score)	0.556/-3.8	0.911/-0.9	
BMD TH (mg/cm^2/z-score)	0.611/-3.6	1.087/+0.4	

BSAP: Bone specific alkaline phosphatase, TMP/GFR: Maximum tubular reabsorption of phosphorus factored for glomerular filtration rate, BMD: Bone Mineral Density, FN: Femoral Neck, TH: Total Hip

Table 1. Baseline and follow-up biochemical and DXA data.

mal. At that time the working diagnosis was tumor induced osteomalacia (TIO). She was treated with high dose phosphate salts (3 gr per day in six divided doses) and alphacalcidol (1 mcg bid) with progressive resolution of the symptoms. Thorough investigation for TIO (including CT, MRI, octreoscan, FDG-PET scan) was negative. Six months later there was complete resolution of the symptoms, improvement of radiology abnormalities, while phosphate levels were improved leading to gradual decrease in the dose of phosphate (2 gr per day in four divided doses) and alphacalcidol (1 mcg once a day). One year later, we were able to determine fibroblast growth factor-23 (FGF23) levels, which were within normal limits [83 RU/ml (n.l.<180 RU/ml)]. At that time phosphate levels were 2.9 mg/dl. Given that result, along with the significant improvement of the patient's clinical and laboratory findings and the diminution of phosphate salt dose (intermittently up to 1 gr per day), late-onset autosomal dominant hypophosphatemic rickets (ADHR) was included in the differential diagnosis. Genetic analysis revealed that our patient was heterozygous for the R176Q mutation of *FGF23* gene, a mutation responsible for ADHR (Figure 1B).

Commentary

ADHR is a rare form of inherited isolated renal phosphate wasting, with X-Linked hypophosphatemic Rickets (XLH) being the most common[1,2]. XLH usually presents with typical signs of rickets in young children, while ADHR is characterized by variable age of clinically evident disease and incomplete penetrance. Two distinct clinical phenotypes based on the age at presentation have been described[1,3]. Early-onset ADHR presents during childhood, characterized by short stature, rickets and lower extremity deformities mimicking XLH, while late-onset ADHR is characterized by normal phosphate levels and growth during childhood, followed by osteomalacia with bone pain, pseudofractures and weakness in adolescence or adulthood, but with no lower extremity deformities. Most of the late-onset ADHR patients are women; pregnancy seems to be a precipitating event, while these two phenotypes can be observed in the same kindred. Furthermore a number of patients may spontaneously resolve the phosphate wasting defect.

ADHR was first described as a phosphate wasting disease with an autosomal dominant inheritance in 1971. Positional cloning studies led to the identification of the gene responsible for ADHR, fibroblast growth factor 23 (*FGF23* gene)[1-3]. Four different mutations have been described, each resulting in amino acid substitutions at a protease cleavage site (RXXR), leading to impaired protease cleavage of mutant FGF-23 molecules. FGF-23, an osteocyte-derived hormone, is frequently elevated in subjects with renal phosphate wasting disorders, such as TIO, XLH, ADHR and polyostotic fibrous dysplasia1. By acting on specific FGFRs with a-klotho as co-factor, FGF23 inhibits renal phosphate reabsorption by decreasing the expression of NaPT2a and NaTP2c co-transporters, suppresses CYP27B1 and increases CYP24 activity, thus reducing calcitriol levels and increasing calcitriol and 25(OH) D catabolism. Furthermore recent evidence indicates that FGF23 might suppress PTH secretion[1].

Control of FGF23 secretion by osteocytes and osteoblasts is still under research[1]. The best documented hormone controlling FGF23 levels is calcitriol, which increases FGF23 levels by acting on specific promoter at the *FGF23* gene. Thus there is an FGF23-calcitriol negative feedback loop. Moreover there is evidence that PTH might also increase FGF23 levels, thus giving rise to another negative feedback axis between FGF23 and PTH. The effect of phosphate *per se* on FGF23 secretion is still unclear, but the positive effect on FGF23 levels seems to be delayed over a couple of days. Finally iron status seems

to modulate FGF23 levels through a yet unknown mechanism[4]. Studies in normal subjects showed inverse relationship between ferritin levels and C-terminal FGF23, while no association was observed with intact FGF23 levels, indicating the increased catabolism of FGF23 maintains appropriate intact FGF23 levels. However in ADHR the observed negative association concerned also the intact molecule, indicating that in some cases the inability to substantially increase the clearance of FGF23 might lead to hypophosphatemia. Thus it is possible that iron deficiency, commonly observed during pregnancy, might explain the precipitating effect of pregnancy in late-onset ADHR, finding that was also observed in our case. Therefore it seems sensible to periodically check for and treat iron deficiency at least in patients with ADHR.

The value FGF23 determination in the various forms of hypophosphatemic disorders is under investigation[1]. Several studies found increased serum FGF23 concentrations in XLH and TIO, pointing to the use of FGF23 measurement in the differential diagnosis of hypophosphatemia. Indeed in cases of FGF23-independent hypophosphatemia, FGF23 levels are depressed or within normal limits. In documented cases of ADHR levels of FGF23 seem to vary with disease activity[5], and FGF23 levels correlate negatively with phosphate primarily in patients with low phosphate concentrations, especially when followed longitudinally. Moreover a number of investigators propose the use of FGF23 measurement in the evaluation of hypophosphatemic disorders, given that in ADHR FGF23 levels may correlate with disease activity and in XLH FGF23 levels increase during treatment due to the effect of calcitriol and phosphate salts. In our case FGF23 determination, though being within normal limits, led to the suspicion of late-onset ADHR. However our oversight not to include at presentation ADHR in the differential diagnosis of hypophosphatemia led to expensive imaging studies, which even if negative could not rule out TIO. Moreover, we must stress that elevated FGF23 at presentation would still indicate either TIO and ADHR. Furthermore while on treatment normal phosphate levels along with normal FGF23 could still not exclude TIO, given the fact that not all TIO cases have elevated FGF23 levels. Thus rigorous evaluation of the patients' history might have led to genetic testing upfront, thus avoiding imaging studies. In any case we believe that FGF23 measurements might prove helpful in the differential diagnosis of hypophosphatemic disorders, provided assay standardization and collection of data from appropriate controls.

Current therapy of hypophosphatemic disorders consists of administration of phosphate salts and vitamin D analogs[1]. Although early initiation improves several aspects of XLH, correction of skeletal deformities is generally incomplete. Furthermore long-term phosphate salt and vitamin D analogue treatment increases the risk of nephrocalcinosis and renal failure and secondary or even tertiary hyperparathyroidism. Thus there is a strong need for new therapeutic approaches. Potential future treatments include the use of C-terminal FGF23 fragment to compete intact FGF23 for the binding to FGFR, monoclonal antibodies against FGF23, use of calcitonin that seems to decrease FGF23 levels and finally inhibition of FGF23 receptor. Recently a phase 1 trial using FGF23 monoclonal antibody (KRN23) in XLH has been completed (ClinicalTrials.gov, NCT00830674), while phase 2 trials are underway (ClinicalTrials.gov, NCT01571596, ClinicalTrials.gov, NCT01340482).

In conclusion this is the first, to our knowledge, reported case of ADHR in Greece. In our case the spontaneous remission of phosphate wasting along with the normal concentrations of FGF23 led to the correct diagnosis, confirmed by the appropriate genetic testing.

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Questions

1. ADHR is always associated with increased FGF23 levels.
A. True
B. False

Critique

False. In ADHR FGF23 levels vary with disease activity. Thus elevated or even inappropriately normal FGF23 levels are observed in patients with active disease, while remission of the phenotype is associated with lower FGF23 levels. Moreover in patients with active ADHR FGF23 levels show negative correlation with phosphate levels, while in normal subjects and in ADHR patients with normal phosphate concentration, FGF23 shows positive correlation with phosphate levels.

2. ADHR is caused by mutations at the cleavage site of FGF23, leading to decreased catabolism.
A. True
B. False

Critique

True. Mutations at the cleavage site of FGF23 result in decreased catabolism, thus prolonging its action. Four different mutations have been described, each resulting in amino acid substitutions at a protease cleavage site (RXXR), leading to impaired protease cleavage of mutant FGF-23 molecules.

3. Iron deficiency seems to decrease FGF23 levels
A. True
B. False

Critique

False. Iron deficiency seems to increase FGF23 production. In the case of intact metabolic clearance, there is increase in C-terminal FGF23 fragments, while in ADHR there is also increase in the intact molecule.