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Case Report

Autosomal dominant hypophosphatemic rickets in an 85 year old woman: Characterization of her disease from infancy through adulthood

Margaret Seton [a,*], Harald Jüppner [b,1]

[a] Massachusetts General Hospital, Rheumatology, Allergy & Immunology, Bulfinch 165, 55 Fruit St, Boston, MA 02114, USA
[b] Massachusetts General Hospital, Endocrine Unit, Thier 10, 55 Fruit St, Boston, MA 02114, USA

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ABSTRACT

Background: Autosomal dominant hypophosphatemic rickets (ADHR) is a rare genetic disorder of phosphate homeostasis characterized, when severely expressed, by osteomalacia, suppressed levels of calcitriol, and renal phosphate wasting due to elevated levels of fibroblast growth factor 23 (FGF23). The disease is caused by heterozygous FGF23 mutations at the RXXR site that prevent cleavage of the intact hormone.
Objectives: An FGF23 mutation was identified in the proband an 85-year-old woman with elevated FGF23 levels, and her clinical course was characterized. Medical records revealed she was treated for rickets as an infant. She was then asymptomatic until soon after her 4th pregnancy, when she suffered incapacitating bone pain and weakness, age 37. Symptoms remitted with brief treatment.
Results: The proband and one son, but not other family members, were found to be heterozygous for the R176Q mutation in FGF23. Expression of this germ line mutation was strikingly different in both individuals in terms of skeletal health, FGF23 levels and disease activity.
Conclusions: The identified FGF23 mutation in two members of this family raises questions about molecular mechanisms that have led to intermittent increases in FGF23 synthesis and secretion, and disease expression.

Introduction

Autosomal dominant hypophosphatemic rickets (ADHR, OMIM #193900) is a rare disorder of phosphate homeostasis resulting from heterozygous point mutations at amino acid residues 176 or 179 in fibroblast growth factor 23 (FGF23) [1]. These mutations disrupt enzymatic cleavage of the protein by a furin-like proprotein convertase, resulting in prolonged activity of this phosphate-regulating hormone [2–4]. In severe cases, ADHR is characterized by impaired mineralization of bone, low serum phosphate due to renal phosphate-wasting, and low or inappropriately normal 1,25-dihydroxyvitamin D3 (calcitriol) levels. These abnormalities are caused by enhanced FGF23 bioactivity, which reduces expression of NPT2a and NPT2c in the proximal renal tubules, and reduces calcitriol levels by diminishing the renal 1α-hydroxylase and increasing the 24-hydroxylase activity [5]. Incomplete penetrance and variable age of onset are described in ADHR, and fluctuations in FGF23 concentration in these patients have been demonstrated that correlate with disease severity. Remissions have been reported [6,7]. The factors responsible for these fluctuations that result in variable disease expression remain unknown.

We herein report a family with ADHR in which the proband, now an 85 year old woman, was described in hospital records to have had rickets as a child, from which she was apparently cured. At age 37, she developed severe osteomalacia due to 'phosphate diabetes,' a condition then defined by excessive urinary phosphate due to a defect in renal tubular reabsorption of phosphate. She was extensively studied at the Massachusetts General Hospital (MGH) by Drs. Nagant de Deuxchaisnes and Krane, and their findings were published in a case series in which she is case 2 [8]. At age 84, she was again evaluated at MGH and a heterozygous FGF23 mutation (R176Q) was identified in her and one of her children, who was said to be 'rachitic' as an infant. This child, now in his 57th year, reached normal adult height with no evidence of disease throughout childhood, adolescence or adulthood. He shows no clinical or laboratory abnormalities in recent testing. This is the longest follow-up reported on an individual affected by ADHR, which gives novel insights into the natural history of this rare disease.

Material and methods

Interviews with the family, clinical history and physical examination of the patient and genetic analysis of the family for the FGF23 mutation were performed at the MGH. The patient's medical records from 1965 were reviewed in detail, and pertinent clinical and laboratory findings described in the original report were extracted. FGF23 levels were measured using an immunometric enzyme assay performed at Mayo Medical Laboratories (Rochester, Minnesota) using methods previously

* Corresponding author. Fax: +1 617 726 2872.
E-mail addresses: mseton@partners.org (M. Seton), jueppner@helix.mgh.harvard.edu (H. Jüppner).
[1] Tel.: +1 617 726 3966.

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described [9]. Mutational analysis of the *FGF23* gene was performed at GeneDx (Gaithersburg, Maryland) for the proband. The authors confirmed this mutation and performed subsequent genetic testing for the identified R176Q mutation in FGF23 in every living family member using described methods [1,10]. Informed consent was obtained from the proband and all participating family members using a protocol approved by Partners Internal Review Board (Boston, Massachusetts).

Results

The proband was born in France in 1926, the 3rd child of non-consanguineous parents. By age 1 1/2 years, her limbs began to bow with weight-bearing, and she was brought to a hospital near Strasbourg for corrective orthopedic surgery by age 4. As detailed in the medical records, she underwent bilateral osteotomies and was casted for 6 months, then wore orthopedic molds on her lower extremities over the next year. Her father's letters describe that throughout her childhood, she was on "a healthy diet, fortifying to the bones," and that "both medications and ultraviolet rays were prescribed." The patient remembers neither illness nor progressive deformity in her youth. In 1945, the patient married an American soldier and immigrated to the United States.

Two years after the birth of her 4th and last child, she began to suffer physical impairments (age 35). She described progressive weakness in her arms and legs, rib pain and difficulty walking. She had been diagnosed with goiter and hypothyroidism a year earlier. At age 37, she was admitted to the MGH. She was taking no medications. She had normal thyroid function, and the following laboratory findings: her hemoglobin was 12.4 mg/dL (reference 12.0–16.0 g/dL); serial serum calcium levels were 9.0, 9.4, and 9.1 mg/dL (reference 8.5–10.5 mg/dL), with serum phosphorus levels of 1.3, 2.1, and 2.4 mg/dL (reference 2.6–4.5 mg/dL), respectively. It is unknown whether these were fasting levels. Tubular reabsorption of phosphate was estimated to be only 85%, when serum phosphorus measured 1.3 mg/dL. Serum iron on admission was 84 μg/dL (reference 50–150 μg/dL).

The patient suffered no significant loss of height between the ages of 37 and 84 years (Table 1). She had the onset of menarche at age 13, and menopause at age 39. At the MGH, she was determined to have severe osteomalacia by bone biopsy, and was diagnosed as suffering from adult phosphate diabetes. There was no evidence of Fanconi's syndrome to account for renal phosphate wasting, no glycosuria or proteinuria, and no evidence for a urinary concentrating defect. Malabsorption was excluded as a cause of hypophosphatemia. Measured Vitamin A and carotene in serum were normal. There was no evidence by history of heavy metal poisoning.

Fasting blood chemistries taken from the patient and her 4 children in 1964 showed no abnormalities in the children's studies. The patient's fasting calcium was 8.8 mg/dL (reference 8.5–10.5 mg/dL) with the serum phosphorus 1.5 (reference 3.0–4.5 mg/dL), and serum alkaline phosphatase 4.9 Bodansky units (reference range: 2.0–6.0 Bodansky units). The patient's extensive laboratory studies during this admission were previously reported [8]. These studies revealed a serum phosphorus that became even lower with dietary restriction of phosphate (measured tubular re-absorption of phosphate 68%); and that was refractory to simple phosphate repletion. It was not until both calcium and neutral sodium phosphate (MGH pharmacy) were given in combination with 50,000 IU ergocalciferol daily that the serum and urinary calcium levels normalized, she entered a positive calcium balance and the serum phosphorus began to rise [8]. Apart from this inappropriate loss of phosphate in the urine, her renal function was normal throughout. We do not have radiographic images any longer, just the written reports from the medical records, which describe pseudofractures in the ribs, pelvis and proximal femurs, with deformity of the pelvis and left femur. The radiograph of the skull was normal.

Table 1
Adult height, year of birth, and birth weight of patient's children.

Family member	Adult height	Year of birth	Birth weight and height
Father	5′ 7″	1892	
Mother	5′ 6″	1901	
Brother	6′ 0″	1923	
Sister	5′ 4″	1925	
Patient I-1 (age 19)	5′ 1″	1926	
(Age 37)	4′ 11″		
(Age 84)	4′ 11″		
Patient's eldest daughter (II-4)[a]		1948	6 lb 9 oz, 21″
Patient's eldest son (II-3)	5′ 9″	1950	6 lb 3 oz, 20.5″
Patient's son FGF23+ (II-2)	5′ 7″	1955	7 lb 10.5 oz, 20″
Patient's youngest daughter (II-1)	5′ 3″	1960	6 lb 13 oz, 19″

[a] Daughter II-4 died age 62; her adult height is unknown.

The patient was discharged on a prolonged trial of oral neutral sodium phosphate, prescribed as 6 capsules (0.3 g) every 3 h. Ingestion of milk and other dairy products were encouraged. The bone pain diminished gradually in her thighs, ribs and shoulders, resolving completely by week 6 of treatment as her muscular strength and gait normalized. The serum phosphorus level at 6 weeks was 3.8 mg/dL 3 h after the last dose of oral phosphorus, and the serum calcium was 9.8 mg/dL. A repeat iliac crest biopsy performed 7 months later showed "a marked reduction in the amount of osteoid seams" [8]. There was radiographic healing of pseudofractures. She chose to cease gradually her phosphate supplements after 3 years. Milk and other dairy products were substituted according to the patient.

There are many insights that were drawn from the 1967 paper (case 2), [8] but two shall be mentioned here. One is the observation that "Her rickets healed in the epiphyses of the extremities that were immobilized in plaster following the osteotomies performed at age four" [8] (healing of immobilized epiphyses in refractory rickets has been described by Tobler et al [11]). The second was the recommendation that phosphorus be dosed every 4 h; this was derived from the observation that this regimen resulted in transient improvements in serum phosphorus that lasted for several hours.

In 2010, she returned to the MGH Rheumatology clinic; she was 84 years old and recovering from a gastrointestinal illness. She was taking calcium carbonate 500 mg with Vitamin D 200 IU 3 times a day with meals. Recent past medical history was notable for an ankle fracture (2009), adult onset diabetes mellitus, hypertension and a myocardial infarction in 2005. The patient's height was 4′ 11″ and she weighed 128 lb (BMI 26.1). Physical examination showed a long torso to lower extremity ratio, with mild kyphoscoliosis. She had a slightly rocking gait due to a leg length discrepancy, and some internal rotation of the right lower extremity, particularly evident at the right knee. The left hip showed no internal or external rotation. Her muscle strength was normal. Early Bouchard's nodes were noted in her hands. There was no bone tenderness.

In 2011, she was found to be heterozygous for a guanine (G) to adenine (A) exchange at codon 176 replacing arginine with glutamine (R176Q), as described in ADHR. [2,4] No DMP1 mutation was identified. A PHEX mutation was not explored. One of her sons (II-2) is also a carrier of the same FGF23 mutation (Fig. 1). We suspect that he had clinical manifestations of rickets as an infant when his mother described him as having a "pigeon chest" and "knock-knees" as a toddler. With cod liver oil, sunlight and adequate nutrition, he remained asymptomatic and his final adult height (5′ 7″) was usual for the family (Table 1). He is currently healthy with normal serum phosphate and FGF23 levels, and he has two healthy children, who are not carriers of the FGF23 mutation. His two living siblings as well as the only daughter of his deceased sister are also healthy and do not carry the FGF23 mutation. Recent laboratory data are shown in Table 2.

Although the medical records document that both Dr. Nagant de Deuxchaisnes, Dr. Krane and subsequent physicians recommended some form of Vitamin D supplementation each time they saw her in the years that followed, it is unclear from her history what she took,