Serum calcitriol levels in a patient with X-linked hypophosphatemia complicated by autosomal dominant polycystic kidney disease

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Abstract Serum calcitriol [1,25(OH)₂D] levels are low normal in the presence of hypophosphatemia in X-linked dominant hypophosphatemic rickets (XLH) due to elevated serum fibroblast growth factor 23 (FGF23) levels. We report a peculiar finding of markedly elevated serum 1,25(OH)₂D levels in a patient with XLH complicated by autosomal dominant polycystic kidney disease (ADPKD) and retinitis pigmentosa (RP). She was diagnosed with XLH, ADPKD and RP at the age of 5, 13 and 15 years, respectively. After the diagnosis of ADPKD, the 1,25(OH)₂D levels increased up to 282 pg/mL treated with a pharmacological dose of 1 α OHD₃ (1 α OHD₃). At the age of 17 years, under a physiological dose, serum 25-hydroxyvitamin D₃ (25OHD₃) and 1,25(OH)₂D levels were 14.0 ng/mL and 93 pg/mL, respectively. With off-therapy for 3 days, the latter decreased to 9 pg/mL with an increased ratio of 24,25-dihydroxyvitamin D₃ (24,25(OH)₂D₃)/25OHD₃. Serum FGF23 and circulating soluble α -klotho (sKlotho) levels were 552 and 873 pg/mL, respectively, with the latter being almost half of the normal control. Since the coexistence of elevated serum

FGF23 and 1,25(OH)₂D levels contradicted the conventional FGF23 actions, we speculated on the possible association of decreased sKlotho with the peculiar vitamin D metabolism, although mechanisms in detail remained unknown.

Keywords Autosomal dominant polycystic kidney disease · Fibroblast growth factor 23 · Soluble α -klotho · Hypophosphatemia · 24,25-Dihydroxyvitamin D₃ · Retinitis pigmentosa

Introduction

X-linked dominant hypophosphatemic rickets (XLH) is characterized by hypophosphatemia, hyperphosphaturia, and vitamin D-resistant rickets [1]. The responsible gene for XLH is the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) [2]. In XLH, serum calcitriol [1,25(OH)₂D] levels were found to be low normal in the presence of hypophosphatemia due to increased serum levels of fibroblast growth factor 23 (FGF23) [3].

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic renal disease transmitted in an autosomal dominant fashion, characterized by bilateral renal cysts. Gene mutations in *PKD1* or *PKD2* are responsible for ADPKD [4]. In addition, a truncated polycystin-2, a product of mutated *PKD2*, was reported to cause retinal degeneration in transgenic rats [5], which accounts for a rare case of disorder consisting of both ADPKD and RP [6].

Recently, elevated serum FGF23 levels in the presence of decreased circulating soluble α -klotho (sKlotho) levels were reported in ADPKD patients [7]. Interestingly,

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hypophosphatemia was observed only in patients with normal sKlotho levels [7]. However, serum 1,25(OH)₂D levels were within the normal ranges in ADPKD patients [8].

FGF23 suppresses the synthesis of 1,25(OH)₂D and promotes its degradation. The action of FGF23 is mediated by the FGF receptors coupled with a full-length transmembrane α klotho [9]. The truncated α klotho is the major form of circulating sKlotho [9]. Moreover, it was reported that sKlotho had its own distinct effect on renal phosphate transport independently of transmembrane α klotho [10]. Therefore, the regulatory mechanism of serum 1,25(OH)₂D levels by FGF23 and sKlotho is complex and intriguing in ADPKD.

Clinical investigations may present useful data to elucidate the mechanism in a rare case of XLH complicated by ADPKD. In this paper, we describe markedly elevated serum 1,25(OH)₂D levels in a patient with these rare disorders who had markedly elevated serum FGF23 and moderately decreased serum sKlotho levels simultaneously.

Case

A 5-year-old girl visited Osaka University Hospital complaining of knock-knees and a short stature (−2.4 SD). She was born healthy and had no problems in the perinatal periods. Laboratory investigations revealed hypophosphatemia (2.2 mg/dL), hyperphosphaturia (TmP/GFR: 2.0 mg/dL), and elevated serum ALP values (1399 IU/L) with rickets based on wrist and knee radiographies. The presence of knock-knees, a short stature in addition to hypophosphatemia, hyperphosphaturia, and elevated serum ALP values with rickets suggested that she was suffering from XLH. There was no consanguinity in her family. According to the inquiry from parents, there seemed to be no metabolic bone diseases in her family, although her mother had no brothers in her siblings. Also, blood and urinary bone markers in her parents were within the normal ranges. Under the clinical diagnosis of a sporadic XLH patient, we began to treat her with a pharmacological dose of 1 α OHD₃ (0.3 μ g/kg/day), and then we gradually reduced the dose in Minoh City Hospital (Fig. 1a). The therapy normalized serum ALP values at the age of 6 years. Phosphate salts (30 mg/kg/day) were added from the age of 8–14 years. A PHEX gene mutation (c.934-1G>A) was confirmed at 15 years old. She was diagnosed with ADPKD and RP at 13 and 15 years, respectively, on the basis of the family history of her father suffering from ADPKD and RP. The clinical criteria for the diagnosis of ADPKD were based on the presence of more than 5

extensive cysts in both kidneys on a plain CT imaging test with a slight calcification in the kidney. She did not have the following extra renal manifestations: cysts in the liver, pancreas and arachnoid membrane; intracranial aneurysms; dolichoectasias; aortic root dilatation and aneurysms; mitral valve prolapse; and abdominal wall hernias. A genetic analysis for ADPKD was not done, because both the patient and her guardian did not agree to this investigation. However, we speculated it to be implausible that she was complicated by another rare genetic disease such as nephronophthisis or Bardet–Biedl syndrome. It was because she neither had proteinuria, glycosuria nor abnormal levels of urinary beta 2 microglobulin excretions (223 ng/ml: 38–497). Our speculations seemed to be confirmed by the fact that she neither had neurological problems nor mental retardation.

At the age of 19 years, the increase in cyst volumes was detected. (Fig. 2). Serum 1,25(OH)₂D levels began to increase after the clinical diagnosis of ADPKD and reached 282 pg/mL at the age of 13 years (Fig. 1b). However, serum Ca (Fig. 1d) and PTH levels (Fig. 1i) were within the normal range, while urinary excretion of Ca showed only a transient elevation (Fig. 1e) on the maximal dose of 1 α OHD₃ (Fig. 1a). Then, the therapy was stopped for 2 weeks and laboratory data were examined: serum phosphate 1.7 mg/dL, TmP/GFR 1.3 mg/dL, 1,25(OH)₂D 7 pg/mL, 25-hydroxyvitamin D₃ (25OHD₃) 10.8 ng/mL, intact PTH 28 pg/mL, intact FGF23 316 pg/mL. Renal functions were within the normal ranges: serum Cr 0.45 mg/dL, BUN 15 mg/dL. By contrast, her father had 37 pg/mL of 1,25(OH)₂D, 11.7 ng/mL of 25OHD₃, and 36 pg/mL of intact PTH. At the age of 17 years, under a physiological dose of 1 α OHD₃ (0.05 μ g/kg/day), serum 25OHD and 1,25(OH)₂D levels were 14.0 ng/mL and 93 pg/mL, respectively. With off-therapy for 3 days, the latter decreased to 9 pg/mL with an increased ratio of 24,25-dihydroxyvitamin D₃ (24,25(OH)₂D₃)/25OHD₃. This value was markedly increased compared with age-matched normal controls [0.202 vs. 0.063 $\pm$ 0.03(SD), respectively, n = 49]. Serum 24,25(OH)₂D₃ and 25OHD₃ levels were, respectively, measured by a high-performance liquid chromatography–tandem mass spectrometry [11]. Also, this increase of 24,25(OH)₂D₃/25OHD₃ ratio was confirmed compared to 5 adult XLH patients treated with 1 α OHD₃ after adjusting by multiple regression analysis as serum 1,25(OH)₂D levels for confounders (P = 0.0065). In addition, serum intact FGF23 and circulating sKlotho levels were 552 and 873 pg/mL, respectively, with the latter being almost half of the normal control [12]. They were measured using ELISA kits produced by Kainos Laboratories Inc., (Tokyo, Japan) and Immuno-Biologic Laboratories (Gunma, Japan), respectively.

Fig. 1 Clinical course of laboratory data during the $1\alpha\text{OHD}_3$ therapy. **a** Dose of $1\alpha\text{OHD}_3$, **b** serum $1,25(\text{OH})_2\text{D}$ levels. Serum $1,25(\text{OH})_2\text{D}$ levels were 7 and 9 pg/mL on the off-therapy, respectively. Symbols of asterisk and double asterisk denoted off-therapy for 2 weeks and 3 days, respectively. **c** Serum FGF23 levels, **d** serum calcium levels, **e** urinary calcium levels, **f** serum ALP levels, **g** Serum phosphate levels, **h** Tmp/GFR values, **i** serum intact PTH levels

Fig. 1 continued

Discussion

We reported peculiar patterns of the vitamin D metabolites in a patient with extremely rare disorders consisting of XLH, ADPKD, and RP (Table 1). The patient showed markedly increased serum $1,25(\text{OH})_2\text{D}$ levels after the

development of renal cysts during the treatment with $1\alpha\text{OHD}_3$. Moreover, serum $1,25(\text{OH})_2\text{D}$ levels were sharply decreased and the $24,25(\text{OH})_2\text{D}_3/25\text{OHD}_3$ ratio was increased after 3-day off-therapy, suggesting the increased catabolism of $1,25(\text{OH})_2\text{D}$ caused by the elevated serum FGF23 levels.

Fig. 2 T2-weighted MRI imaging test at the age of 19 years. Note the enlarged cysts in both the kidneys

This was an unexpected observation, because the serum 1,25(OH)₂D levels in patients with XLH are usually at the low normal ranges. Elevated levels of FGF23 contribute to inhibit 25OHD-1 α -hydroxylase in the kidney to decrease 1,25(OH)₂D synthesis [3]. Thus, the markedly increased

serum 1,25(OH)₂D levels in this patient seem to be caused by the blocking of the conventional FGF23 actions. Actually, the 1,25(OH)₂D level was comparable to or even more than levels reported in patients with XLH after the treatment with neutralizing antibody against FGF23 [3]. However, the rapid decrease of 1,25(OH)₂D level after the off-therapy with 1 α OHD₃ associated with conversion of 24,25(OH)₂D₃ was not explained by the decreased action of FGF23.

We speculate that the rare complication of ADPKD in this patient with XLH which developed at the age of 13 years may account for the blocking of FGF23 actions, because patients with ADPKD have been reported to show decreased levels of sKlotho [7]. Recently, sKlotho has been shown to exhibit a distinct effect on renal phosphate transport [10] and calcium reabsorption in the renal distal tubules independent of FGF23 actions [13]. In addition, these effects were suggested to be mediated by β -glucuronidase and sialidase associated with sKlotho, respectively [10, 13]. Thus, it is plausible that these mechanisms rather than classical action of FGF23 are linked to the peculiar observation of abnormally increased serum 1,25(OH)₂D levels even in the presence of elevated serum FGF23 levels in this patient. However, we have no data directly related to these actions of sKlotho in this patient.

One might argue that the extremely high levels of serum 1,25(OH)₂D levels in this case were caused by the pharmacologically treated dose of 1 α OHD₃. It is possible that

Table 1 Summary of laboratory data for the present case

	XLH	ADPKD	Present case
1,25(OH) ₂ D	➡ or ⬇	➡	⬆⬆
FGF23	⬆	➡ or ⬆	⬆⬆
s-Ca	➡	➡	➡
u-Ca	➡	➡	➡ or ⬆
ALP	⬆⬆	➡	⬆⬆ to ➡
s-Pi	⬇⬇	➡ or ⬇	⬇
TmP/GFR	⬇⬇	➡ or ⬇	⬇
PTH	➡ or ⬆	➡	➡

➡: normal
⬆: increased
⬇: decreased
⬆⬆: markedly increased
⬇⬇: markedly decreased

the given dose affected the data; however, the dose effect did not explain that serum $1,25(\text{OH})_2\text{D}$ level was still high (93 pg/mL) in response to hypophosphatemia under a physiological dose of $1\alpha\text{OHD}_3$ (0.05 $\mu\text{g/kg/day}$). In addition, $1,25(\text{OH})_2\text{D}$ level decreased to 9 pg/mL by off-therapy for 3 days. Then, serum $1,25(\text{OH})_2\text{D}$ levels increased gradually again under a physiological dose of $1\alpha\text{OHD}_3$ (Fig. 1b) in spite of the extremely increased serum FGF23 levels (Fig. 1c). The reason for the change of the $1,25(\text{OH})_2\text{D}$ levels remains unexplained.

In this patient, TmP/GFR values decreased only slightly (Fig. 1h) in the presence of extremely high serum FGF23 levels after the age of 15 years (Fig. 1c). This was compatible with the observation that hypophosphatemia is only observed in ADPKD patients with normal sKlotho and elevated FGF23 levels [7]. Thus, a decrease of sKlotho levels possibly acted to ameliorate phosphate leak through its original effect on phosphate transport other than the traditional action of FGF23 through transmembrane αklotho associated with FGF23 receptors.

We did not detect hypercalcemia during the $1\alpha\text{OHD}$ therapy for a long period (Fig. 1d) in spite of the presence of markedly elevated serum $1,25(\text{OH})_2\text{D}$ levels (Fig. 1b). One of the possible explanations was the increased urinary excretion of calcium due to decreased sKlotho levels [13]. However, it was not the case because urinary calcium excretion was almost within the normal range after the age of 12 years (Fig. 1e) when the serum $1,25(\text{OH})_2\text{D}$ levels were extremely elevated (Fig. 1b). Thus, some other mechanisms of vitamin D resistance might be associated, as previously reported [14]. Further research is necessary to elucidate the mechanism.

In conclusion, a long period of clinical observation in a rare case of XLH complicated by ADPKD and RP for almost 15 years suggested the possible presence of a contribution of sKlotho on serum $1,25(\text{OH})_2\text{D}$ levels, although the precise mechanism of this regulation needs further investigation.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB Approval Number 11000515) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26:1381–8.
2. Francis F, Hennig S, Korn B, Reinhardt R, de Jong P, Poustka A, Lehrach H, Rowe PSN, Goulding JN, Summerfield T, Mountford R, Read AP, Popowska E, Pronicka E, Davies KE, O'Riordan JLH, Econs MJ, Nesbitt T, Drezner MK, Oudet C, Pannetier S, Hanauer A, Strom TM, Meindl A, Lorenz B, Cagnoli B, Mohnike KL, Murken J, Meitinger T. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. *Nat Genet.* 1995;11:130–6.
3. Carpenter TO, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Wooddell MM, Kawakami T, Ito T, Zhang X, Humphrey J, Insogna KL, Peacock M. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. *J Clin Invest.* 2014;124:1587–97.
4. Chapman AB, Devuyt O, Eckardt KU, Gansevoort RT, Harris T, Horie S, Kasiske BL, Odland D, Pei Y, Perrone RD, Pirson Y, Schrier RW, Torra R, Torres VE, Watnick T, Wheeler DC, Participants Conference. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a kidney disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2015;88:17–27.
5. Gallagher AR, Hoffmann S, Brown N, Cedzich A, Meruvu S, Podlich D, Feng Y, Könecke V, de Vries U, Hammes HP, Gretz N, Witzgall R. A truncated polycystin-2 protein causes polycystic kidney disease and retinal degeneration in transgenic rats. *J Am Soc Nephrol.* 2006;17:2719–30.
6. Koçyigit I, Unal A, Ozaslan E, Oymak O, Utas C. Does retinitis pigmentosa relate with polycystic kidney disease? *Int Urol Nephrol.* 2010;42:1103–5.
7. Pavik I, Jaeger P, Ebner L, Poster D, Krauer F, Kistler AD, Rentsch K, Andreisek G, Wagner CA, Devuyt O, Wüthrich RP, Schmid C, Serra AL. Soluble klotho and autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol.* 2012;7:248–57.
8. Pavik I, Jaeger P, Kistler AD, Poster D, Krauer F, Cavelti-Weder C, Rentsch KM, Wüthrich RP, Serra AL. Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate. *Kidney Int.* 2011;79:234–40.
9. Xu Y, Sun Z. Molecular basis of Klotho: from gene to function in aging. *Endocr Rev.* 2015;36:174–93.
10. Hu MC, Shi M, Zhang J, Pastor J, Nakatani T, Lanske B, Razzaque MS, Rosenblatt KP, Baum MG, Kuro-o M, Moe OW. Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. *FASEB J.* 2010;24:3438–50.
11. Tsugawa N, Suhara Y, Kamao M, Okano T. Determination of 25-hydroxyvitamin D in human plasma using high-performance liquid chromatography–tandem mass spectrometry. *Anal Chem.* 2005;77:3001–7.
12. Carpenter TO, Insogna KL, Zhang JH, Ellis B, Nieman S, Simpson C, Olear E, Gundberg CM. Circulating levels of soluble klotho and FGF23 in X-linked hypophosphatemia: circadian variance, effects of treatment, and relationship to parathyroid status. *J Clin Endocrinol Metab.* 2010;95:E352–7.

13. Cha SK, Ortega B, Kurosu H, Rosenblatt KP, Kuro-O M, Huang CL. Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1. *Proc Natl Acad Sci USA*. 2008;105:9805–10.
14. Yamamoto T, Seino Y, Tanaka H, Yamaoka K, Kurose H, Ishida M, Yabuuchi H. Effects of the administration of phosphate on nuclear 1,25-dihydroxyvitamin D3 uptake by duodenal mucosal cells of Hyp mice. *Endocrinology*. 1988;122:576–80.