

Overlap of Pseudohypoparathyroidism and Primary Hyperparathyroidism in a Patient: Just a Coincidence?

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ABSTRACT

A 56-year-old female patient with the phenotype of Albright's hereditary osteodystrophy (AHO) and pseudohypoparathyroidism 1a (PHP) diagnosed in 1987 was shown to have a heterozygote inactivating mutation on the GNAS1 gene. The patient has been treated with oral calcium and vitamin D since diagnosis of PHP 1a and developed primary hyperparathyroidism (pHPT) in 2009. Ultrasound as well as 99Tc-sestamibi could demonstrate a lesion in the right lower position. Intraoperatively, a solitary parathyroid adenoma was found and resected leading to a 'normalization' of PTH and calcium. This case highlight is the rare coincidence of PHP, AHO and pHPT.

Keywords: Pseudohypoparathyroidism, Primary hyperparathyroidism.

CASE REPORT

A 56-year-old-female patient with the phenotype of Albright's hereditary osteodystrophy (AHO) and pseudohypoparathyroidism Type 1a (PHP) diagnosed in 1987, was found to have a heterozygote inactivating deletion exon 7 to exon 13 GNAS 1 gene. Family history is unknown due to an adoption (Fig. 1).



Fig. 1: A 56-year-old female patient with the phenotype of AHO

At age 12, hypothyroidism was diagnosed and she was treated with levothyroxine. At age 33, AHO and PHP 1a were diagnosed because of the characteristic phenotype: Short stature, round face, short neck, mental retardation, arterial hypertension, dilatative cardiomyopathy, nephrocalcinosis, calcinosis of the skin and calcinosis in both cerebral hemispheres and the biochemistry: Serum calcium 1.84 mmol/l (2.0-2.6 mmol/l), serum phosphorus 1.20 mg/dl (0.8-1.55 mmol/l), parathyroid hormone (PTH) 392 pg/ml (15-65 pg/ml), 25-OH-Vitamin D3 8.0 ng/ml (> 20 ng/ml). She was treated with calcium and colecalciferol.

At age 49, she was first diagnosed by an endocrinologist. The antithyroid antibody level (TPO) was 1170 U/l (0-35 IU/ml) suggesting Hashimoto thyroiditis. She was treated with levothyroxine 150 µg/ml. No vitamin D3 was given at that time and the 1.25 OH vitamin D3 level was 8.9 pg/ml (18-62 ng/ml). Under a medication of calcium 1.2 g serum calcium was 2.1 mmol/l and PTH 672 pg/ml. She received colecalciferol 1.5 mg and calcium substitution was ceased. Six months later PTH was 66 pg/ml, but increased up to 1000 pg/ml in 2006 and declined spontaneously (Fig. 2). Vitamin D3 level was very low in this period and therefore it was suggested that she did not take vitamin D3 regularly. In January 2009, there was an increase of PTH to nearly 2000 pg/ml and of serum calcium to 2.7 mmol/l. Vitamin D3 therapy was interrupted. Hyperparathyroidism was diagnosed. High osteocalcin level (> 100 ng/ml, 2-22 ng/ml) and high

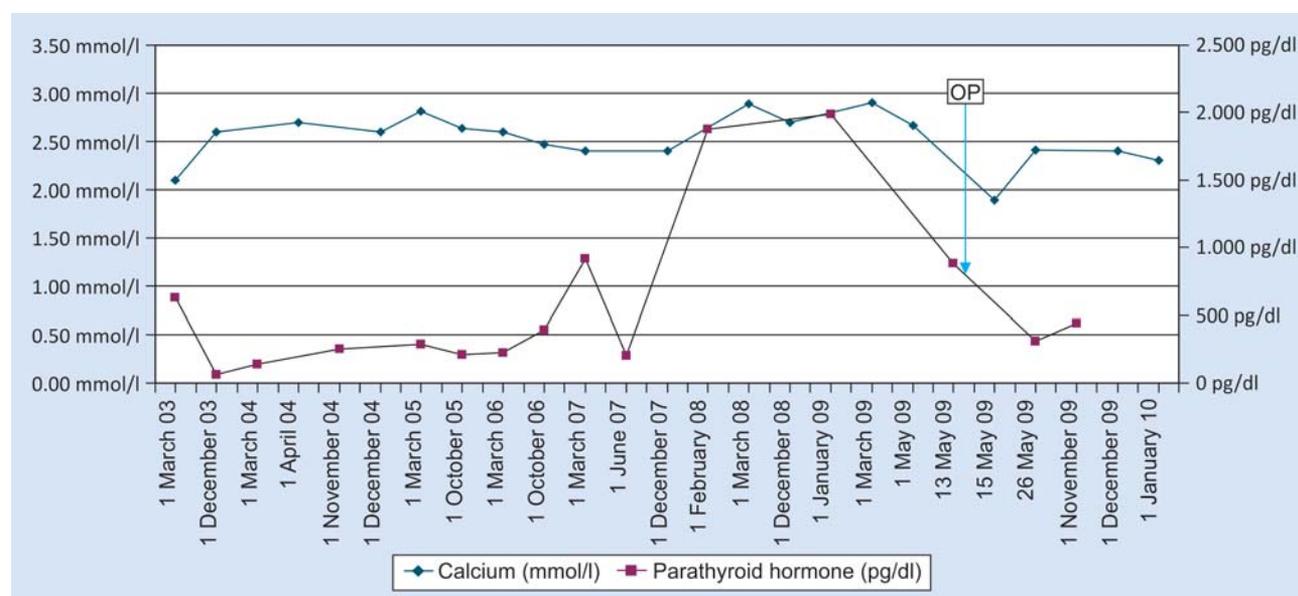


Fig. 2: Parathyroid hormone (pg/ml) and calcium (mmol/l) levels from March 2003 to January 2010

alkaline phosphatase level (206 U/l, 35-104 U/l) indicated elevated bone turnover. Ultrasound of the neck was negative but ⁹⁹Tc-sestamibi scintigraphy could demonstrate a lesion in the right lower position. The thyroid gland did not show any nodules and was small due to chronic thyroiditis.

Intraoperatively, a solitary parathyroid adenoma was detected in the right lower position. The other three parathyroid glands were not enlarged. It was removed leading to a more than 50% decrease of the intraoperative PTH level indicating a successful operation. The enlarged parathyroid gland had a weight of 2.6 gm and was 3 × 2 × 0.9 cm in size. It showed a nodular transformation of chief cells and was classified as a parathyroid adenoma.

The postoperative PTH level decreased to 350 pg/ml, the normal preoperative value for this patient. Serum calcium decreased to 2.1 mmol/l.

DISCUSSION

PHP is a heterogeneous group of disorders whose common feature is parathyroid hormone resistance (PTH). It is generally classified as types 1a, 1b, 1c, 2 according to different phenotypes and pathogenesis.^{2,11} The Albright's hereditary osteodystrophy (AHO) is a syndrome characterized by several distinct physical features, including short stature, obesity, round face, subcutaneous ossifications, brachydactyly and other skeletal anomalies.⁸ Both the PHP 1a and the AHO depend on a heterozygote inactivating mutation on the GNAS1 gene.⁹ Primary hyperparathyroidism is not associated with this gene. The coincidence of PHP 1a and AHO and pHPT is a rarity. There are two cases with a coexisting primary hyperparathyroidism and AHO so far.^{1,10}

In addition to PTH resistance patients with pPHP present TSH resistance.¹² The resistance is generally mild with only minimally elevated TSH levels. Our patient was under levothyroxine substitution since the age of 12 years suggesting TSH resistance. When she was first diagnosed by an

endocrinologist at age 49, the antithyroid antibody level was very high suggesting Hashimoto thyroiditis as well.

PTH resistance in the kidney in PHP 1a is characterized by elevated PTH levels together with hypocalcemia and hyperphosphatemia. A low formation rate of 1.25 OH vitamin D3 together with hyperphosphatemia are contributing to hypocalcemia.⁷ Lack of 1.25 OH vitamin D3 induces secondary hyperparathyroidism, a phenomenon, well known in patients with kidney insufficiency. An early substitution of 1.25 OH vitamin D3 should maintain PTH levels in normal range.^{5,7} A PTH level of 350 pg/ml suggests insufficient vitamin D substitution, being the case in our patient.

The clinical manifestations on bone are variable in PHP 1a and range from normal bone to decreased bone density to osteitis fibrosa cystica to osteosclerosis.³⁻⁶ Whether this variability is a result in the extent of skeletal manifestations to PTH or to differences in the extent of skeletal resistance to PTH or to differences in the circulating levels of PTH and/or 1.25 OH vitamin D3 is still unclear.⁷ Long et al could demonstrate normal bone mineral density and normal bone turnover markers in 22 children and adults with pPHP1a. In our patients, high bone turnover was parallel to high PTH levels of > 2000 pg/ml indicating hyperparathyroidism.

Pathophysiology of the PTH resistance in the kidney makes secondary hyperparathyroidism much more likely than primary hyperparathyroidism. Intraoperatively, however, we found one single adenoma—which was preoperatively detected in ⁹⁹Tc-sestamibi scintigraphy—and three normal glands and, therefore, we supposed primary hyperparathyroidism. The pathophysiology of developing a single adenoma remains to be clarified.

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