CASE REPORT

Pseudohypoparathyroidism: a rare but important cause of hypocalcaemia

Pui Lin Chong, Darryl R Meeking

Academic Department of
Diabetes and Endocrinology,
Portsmouth Hospitals NHS
Trust, Portsmouth, UK

Correspondence to

Dr Pui Lin Chong,
lina.chong@porthosp.nhs.uk

SUMMARY

We present a 46-year-old Caucasian lady with symptomatic hypocalcaemia. Investigations revealed markedly raised parathyroid hormone (PTH) levels with vitamin D deficiency. A number of conditions causing secondary hyperparathyroidism were ruled out from her medical history and initial investigations. The main differential diagnoses were vitamin D deficiency and PTH resistance (pseudohypoparathyroidism, PHP). With high-normal serum phosphate and normal alkaline phosphatase, and a lack of symptoms associated with osteomalacia, vitamin D deficiency alone was unlikely to be the cause of hypocalcaemia. Given a normal physical appearance, genetic testing was arranged and confirmed the diagnosis of PHP type Ib. She is currently taking activated vitamin D to maintain calcium homeostasis. PTH resistance is the hallmark of PHP, a rare complex genetic disorder, which can be easily missed resulting in potentially serious consequences.

BACKGROUND

Pseudohypoparathyroidism (PHP) is a rare heterogeneous group of disorders characterised by end-organ resistance to parathyroid hormone (PTH), in which other hormonal deficiencies such as hypothyroidism and hypogonadism may coexist. It is essential to diagnose PHP so that appropriate genetic counselling and prompt hormonal replacement are offered to affected individuals and their first-degree relatives. This case highlights a rare but important cause of hypocalcaemia.

CASE PRESENTATION

A 46-year-old Caucasian lady was referred with a 2-week history of facial twitching and hand spasms. She denied gastrointestinal and urinary symptoms. There was no family history of note. Her medical history included Asperger's syndrome, obsessive compulsive disorder, anxiety attacks and drug dependence. She had suboptimal intake of calcium and vitamin D, and limited sun exposure. On examination, she demonstrated positive Chvostek's and Trousseau's signs.

INVESTIGATIONS

Blood investigations (table 1) revealed marked hypocalcaemia (1.55 mmol/l), high-normal serum phosphate (1.26 mmol/l), low vitamin D (6.7 µg/l) and markedly elevated PTH (52.2 pmol/l). ECG showed prolonged corrected QT interval.

DIFFERENTIAL DIAGNOSIS

We were able to exclude a number of causes of hypocalcaemia from her history, examination and baseline investigations. These included no recent thyroid or parathyroid surgery, drug causes, hypomagnesaemia or acute pancreatitis (figure 1).

The main differential diagnoses of hypocalcaemia with secondary hyperparathyroidism were vitamin D deficiency and PTH resistance (PHP). To distinguish between the two conditions following treatment of acute symptomatic hypocalcaemia, loading with vitamin D and subsequent resolution of secondary hyperparathyroidism and normalisation of serum calcium would point to a diagnosis of vitamin D deficiency. Vitamin D deficiency mimicking PTH resistance has been described¹ but alone rarely causes significant hypocalcaemia without a rise in ALP. PHP was considered as it corresponded with our patient's biochemical picture of hypocalcaemia and high-normal phosphate level. Measurements of cyclic AMP and urine phosphate following PTH infusion were not performed due to practical reasons.

TREATMENT

She was initially treated with intravenous calcium gluconate followed by oral calcichew and alfacalcidol. She was discharged on calcichew three tablets three times daily and alfacalcidol 2 µg daily.

OUTCOME AND FOLLOW-UP

On endocrine follow-up 4 weeks after discharge, she remained well with normalisation of serum calcium and PTH. Two months later, she was readmitted to the Medical Assessment Unit with a 2-day history of nausea and headache. Her serum biochemistry revealed marked hypercalcaemia—adjusted Ca 3.34 mmol/l, phosphate 1.39 mmol/l, creatinine 251 µmol/l and urea 15.4 mmol/l. Following intravenous fluid replacement her adjusted calcium returned to normal (2.44 mmol/l) and her acute kidney injury resolved (creatinine 87 µmol/l). Her replacement calcium and vitamin were stopped on discharge.

Three weeks later, her intact PTH started to rise (21.2 pmol/l) and there was a concurrent fall in adjusted calcium (2.09 mmol/l). Alfacalcidol (1 µg) and calcichew (one tablet three times) daily were restarted. Currently, she is maintained on just 0.25 µg alfacalcidol daily. This dose is achieving calcium-phosphate homeostasis.

Of note, she did not exhibit the classic phenotype seen in PHP type Ia (PHPIa).² A blood sample was sent for molecular genetic analysis which

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Table 1 Results of initial blood tests

Investigations	Day 1	Day 2	Day 3
Adjusted calcium (2.15–2.60 mmol/l)	1.55	1.91	1.96
Phosphate (0.80–1.50 mmol/l)	1.26	1.58	0.95
Intact PTH (0–6.4 pmol/l)	52.2	42.2	
25(OH) D3 (10–40 µg/l)		6.7	
Magnesium (0.74–1.03 mmol/l)	0.77	0.80	0.80
Urea (3–7.6 mmol/l)	7.0		
Sodium (135–146 mmol/l)	136		
Potassium (3.5–5 mmol/l)	2.9		
Creatinine (45–90 mol/l)	60		
Alkaline phosphatase (30–130 iu/l)	99		

PTH, parathyroid hormone.

Table 2 Classification of pseudohypoparathyroidism⁴

Types	Hormone resistance	AHO	Response to PTH
PHPIa	PTH, TSH, GnRH, GHRH	Present	Blunted cAMP and urine PO_4^{3-} excretion
PHPIb	PTH (±TSH)	Absent	Blunted cAMP and urine PO_4^{3-} excretion
PHPIc	PTH, TSH, GnRH	Present	Blunted cAMP and urine PO_4^{3-} excretion
PPHP	None	Present	Normal response
PHPII	None	Absent	Normal cAMP response, blunted urine PO_4^{3-} excretion

AHO, Albright's hereditary osteodystrophy; GnRH, gonadotropin-releasing hormone; GHRH, growth hormone-releasing hormone; PHPII, pseudohypoparathyroidism type II; PHPIa, PHP type Ia; PHPIb, PHP type Ib; PHPIc, PHP type Ic; PPHP, pseudoPHP; PTH, parathyroid hormone; TSH, thyrotrophin-secreting hormone.

confirmed a diagnosis of PHP type Ib (PHPIb). She was referred to the regional genetics team and has been advised to inform her first-degree relatives of her diagnosis so they may consider biochemical and genetic testing.

DISCUSSION

PHP is a rare genetic disorder characterised by hypocalcaemia and hyperphosphataemia secondary to PTH insensitivity. A prevalence of 3.4/million has been reported.³

The molecular defect lies in the GNAS gene encoding the α -subunit of the stimulatory G protein (G α). Several variants have been identified and the current classification of PHP is shown in table 2.⁴ The following discussion will focus on the two more commonly described subtypes of PHP type I—PHPIa and PHPIb.

Characteristics of PHPIa and PHPIb

The presence of the Albright's hereditary osteodystrophy (AHO) phenotype differentiates PHPIa from PHPIb (table 2).

AHO is a term used to describe a constellation of skeletal and developmental abnormalities. These include brachydactyly (classically shortened 3rd, 4th and 5th metacarpals), heterotrophic ossification, round facies, short stature, central obesity and mental retardation.²

Renal PTH resistance is the hallmark of PHP type I. The defect is localised in the proximal tubule where activated 1,25-dihydroxy D3 is formed from 1 α hydroxylation of 25 hydroxy D3. This process requires PTH stimulation. 1,25-dihydroxy D3 enhances absorption of calcium and phosphate from the gut. Impaired 1,25-dihydroxy D3 formation, coupled with hyperphosphataemia from reduced urine phosphate excretion, leads to hypocalcaemia.⁴

As the distal renal tubule is unaffected, urine calcium reabsorption remains intact and affected individuals are protected from renal stone formation and renal dysfunction. Caution should be exercised with vitamin D and calcium replacement as excessive replacement can cause hypercalcaemia and acute kidney injury. Skeletal responsiveness to PTH is

Figure 1 Initial investigations and causes of hypocalcaemia.²

PTH = parathyroid hormone; Mg^{2+} = magnesium

largely preserved so these patients are at risk of hyperparathyroid bone disease.⁵

Patients with PHPIa may develop resistance to other hormones which act via Gs-coupled receptors such as thyrotrophin-secreting hormone (TSH),⁶ gonadotrophins,⁷ and growth hormone (GH)-releasing hormone.⁸ The age of presentation and the severity of resistance vary greatly but mild hypothyroidism, growth hormone deficiency, delayed puberty or infertility can occur. Those with PHPIb typically have renal PTH resistance alone although TSH resistance has been reported.^{6,9}

Response to exogenous PTH

Upon binding of PTH to PTH receptor that is coupled with the Gs, Gs stimulates adenylate cyclase (AC) which in turn catalyses the formation of cAMP from ATP. PTH resistance in PHP type I can be elicited by a blunted cAMP and phosphatauric response to exogenous PTH due to a defect in the PTH receptor-AC system.

Genetic abnormality

PHP type I is inherited in an autosomal-dominant manner; however, PHPIb may occur sporadically. The human GNAS gene is located on chromosome 20q13 and defects are heterogenous and complex.² Several loss-of-function mutations have been identified in PHPIa.⁴ These mutations lead to impaired Gs protein activation of AC upon (PTH) binding to its receptor, leading to end-organ resistance to PTH. Only maternal transmission of the disease leads to the expression of PHPIa phenotype while paternal transmission is associated with pseudo-PHP¹⁰ defined by the presence of AHO features without hormonal resistance.¹¹

The genetic defect for PHPIb was mapped to chromosome 20q13.3.¹² PHPIb is predominantly caused by the loss of imprinting at differentially methylated regions (DMR) on the GNAS gene which lead to decreased Gs α transcription in the renal proximal tubules, hence tissue resistance to PTH locally.¹³

The genetic analysis on our patient revealed a complete loss of maternal methylation pattern at the GNAS exon 1A DMR and NESP55 DMR and partial loss of maternal methylation at the NESPAS DMR consistent with reported loss of imprinting identified in PHPIb. It has been suggested that sporadic form of PHPIb is caused by imprinting defects in NESP55 and NESPAS DMRs as well as exon 1A DMR, whereas the familial form is a result of imprinting defects in exon 1A DMR and STX16 mutation.¹⁴ With that in mind, our patient may have the sporadic form of PHPIb, supported by the lack of family history.

Management

Annual measurement of serum PTH, calcium, phosphate, thyroid function and urinary calcium is recommended. Plain radiographs of the hands may be useful to confirm shortening of metacarpals. Treatment of hypocalcaemia requires active vitamin D replacement with or without calcium supplements, aiming to normalise serum calcium and serum PTH. Baseline bone densitometry will help reveal the extent of any bone mineral loss.⁶

Individuals with PHPIa should be screened for hypothyroidism, hypogonadism and GH deficiency. This is particularly important in children whose growth and pubertal development may be affected.

Genetic counselling is an important given hormonal deficiencies associated with PHP type I. Pre-pregnancy counselling of affected individuals will ensure they are fully aware of the risks of disease transmission to the fetus and potential effects on the affected child.

Learning points

- In general, causes of hypocalcaemia may be categorised according to those with high-serum parathyroid hormone, PTH (disorders resulting in secondary hyperparathyroidism or due to PTH resistance) and low-serum PTH (disorders primarily related to impaired function of parathyroid glands)—figure 1.
- There are several variants of pseudohypoparathyroidism (PHP) resulting in a clinically diverse disorder with varying degree of hormonal resistance and skeletal manifestations.
- The mainstay of treatment for PHP is activated vitamin D and calcium replacement.
- Owing to excessive PTH action on bones, there is a risk of developing hyperparathyroid bone disease. Treatment should be aimed at normalising serum PTH to minimise such risk.
- There is little risk of renal calculi formation and these patients usually have preserved renal function so vitamin D and calcium replacement can be safely administered to achieve normocalcaemia.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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