Osteoporosis International (2024) 35:737–740
https://doi.org/10.1007/s00198-023-07006-z

CASE REPORT

Falsely elevated parathyroid hormone in a patient with osteoporosis: a case report and review

Kevin McCarroll[1,2] · Donal Fitzpatrick[1,2] · Margaret McCormack[3] · Sabah Abdelfadil[3] · Vivion Crowley[3] · Rosaleen Lannon[1,2] · Martin Healy[1,2]

Received: 30 October 2023 / Accepted: 18 December 2023 / Published online: 28 December 2023

Abstract

Background Parathyroid hormone (PTH) measurements can be falsely elevated due to the hormone binding to other molecules (macro-PTH) or immunoassay interference with heterophile, human anti-animal or other antibodies. This is rare but could lead to incorrect diagnosis, unnecessary investigations or avoidance of teriparatide treatment. We report a case of falsely high PTH levels due to assay interference and review the literature on cases of spuriously elevated PTH.

Case report An 87-year-old woman attending our bone health clinic with osteoporosis had persistently elevated PTH (383–784 pg/ml) using the Roche Cobas e801 immunoassay despite having normal serum calcium, phosphate, 25 hydroxyvitamin D (> 50 nmol/l) and eGFR (> 60 ml/min). To rule out falsely elevated PTH, a polyethylene glycol precipitation (PEG) test was performed which recovered less than 10% of the hormone resulting in a normal level. PTH was also tested on a different assay (Atellica Siemens) that identified a result of 27 pg/ml. The findings were consistent with immunoassay interference likely due to heterophile antibodies giving rise to a spuriously high PTH.

Discussion The presence of unexpectedly high PTH levels should alert physicians to the possibility of false results due to assay interference or macro-PTH. This highlights the importance of clinically correlating results and of good communication with the testing laboratory.

Summary Here, we present the case of an 87-year-old woman with spuriously elevated PTH levels due to immunoassay interference likely mediated by heterophile antibodies. The presence of unexpectedly high PTH levels should prompt consideration of the possibility of false results due to assay interference or macro-PTH.

Keywords Heterophile · Osteoporosis · Parathyroid hormone

Introduction

The accurate measurement of parathyroid hormone (PTH) is essential in diagnosing primary and secondary hyperparathyroidism. The majority of patients with primary hyperparathyroidism are hypercalcaemic and have an elevated or non-suppressed PTH. However, a small proportion is normocalcaemic with a raised PTH in the absence of other causes of high PTH. In secondary hyperparathyroidism, an elevated PTH occurs in the presence of low or low/normal calcium [1]. In all these cases, correct evaluation of PTH is crucial for diagnosis. However, PTH measurements can rarely be falsely elevated due to immunoassay interference with heterophile, human anti-animal or other antibodies [2]. This could lead to unnecessary investigations, incorrect diagnosis and avoidance of parathyroid hormone analogue therapies. Here, we report a patient with osteoporosis and spuriously elevated PTH levels due to assay interference, most likely resulting from heterophile antibodies. We also review the literature on previously reported cases of falsely elevated PTH and their causes.

Kevin McCarroll and Donal Fitzpatrick are joint first authors.

✉ Donal Fitzpatrick
dfitzpatrick939@gmail.com

[1] Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland

[2] School of Medicine, Trinity College Dublin, Dublin, Ireland

[3] Biochemistry Department, St James's Hospital, Dublin, Ireland

Case presentation

The patient was an 87-year-old woman who was initially seen at our bone health clinic in St James's Hospital in 2019 and started on denosumab for severe osteoporosis with multiple vertebral fractures (L1, T8, T12). Table 1 illustrates her biochemistry results with PTH measured on the Roche Cobas e801 electrochemiluminescence immunoassay analyser. PTH was found to be consistently elevated (range: 383 to 784 pg/m) between 2019 and 2023 despite normal serum calcium, 25(OH)D (> 50 nmol/l) and eGFR (> 60 ml/min. A falsely elevated PTH was suspected, and a PTH sample in 2023 was subjected to polyethylene glycol (PEG) 6000 precipitation with the result corrected for dilution. Equal volumes of the PEG precipitation reagent and serum were combined, then incubated for 10 min at room temperature and centrifuged, with less than 10% of hormone being recovered resulting in a normal PTH (37 pg/ml). Serial dilutions were also performed, demonstrating linearity and raising the possibility of macro-PTH. To further investigate, serum PTH was tested on a different platform (Atellica Siemens) that returned a normal level of 27 pg/ml. The patient had kept a dog but had no exposure to other animals, no autoimmune disease and had never undergone treatment with animal monoclonal antibodies, suggesting heterophile antibodies as a cause of assay interference. Table 2 refers to previously published reports of falsely elevated PTH.

Discussion

This case adds to the rare reports of falsely elevated PTH in the literature. Most are due to interference with heterophile or human anti-animal antibodies (HAAA) [3–6, 8–14]. These bind to the animal antibodies in the immunoassay that attach to the PTH, resulting in higher reported levels. Specifically, HAAA is a monospecific, high-affinity antibodies (usually IgG, IgA or IgM) against animal immunoglobulins that may result from prior exposure to animals or from treatment with animal monoclonal antibody therapies [18]. Reported prevalence varies widely (up to 11.7%) [2] though interference with assays is rare with human anti-mouse antibodies (HAMA) most commonly implicated [18, 19]. Heterophile antibodies are previously referred to all interfering antibodies, but the term is now limited to those that develop in response to no clear immunogen [18, 19]. They are weakly polyspecific but can react with antibodies from different animal species though generally give less pronounced interference than HAMA [18].

Table 1 Biochemical results

Blood test	2019	2021	2022	2023	Reference
PTH (pg/ml)	383	784	479	452	15–65
Calcium (mmol/l)	2.31	2.44	2.44	2.45	2.20–2.50
Phosphate (mmol/l)	1.03	1.43	1.13	1.35	0.80–1.20
eGFR (ml/min)	72	82	74	71	≥ 60
25(OH)D (nmol/l)	67	68	53	73	≥ 50
ALP (IU)	47	118	41	56	30–120
CTX (ng/ml)	0.06	0.05	0.04	-	0.016–0.573*

PTH parathyroid hormone (Elecsys Roche assay), *eGFR* (calculated using MDD formula), *ALP* alkaline phosphatase, *25(OH)D* 25 hydroxyvitamin D (LCMS), *CTX* C-terminal telopeptide

*pre-menopausal range

In most cases of assay interference (as in our patient), PTH was elevated to multiple times the upper limit of normal to extremely high (> 5000 pg/ml). However, in one case attributed to heterophile antibodies, there was only a modestly raised PTH (110 pg/ml) [13]. Cavalier et al. in a series of 743 patients with elevated PTH found an interference rate of 4.5% due to HAMA or rheumatoid factor (RF) [20]. However, the effect on PTH levels in many patients was small (mean decline of 29%) when HAMA was removed and 49% (range 0–90%) after removing RF. Overall, in 52.9% of patients' serum, PTH normalised, though the remaining abnormal results may not necessarily imply a pathological level [2].

Interestingly, spurious elevations in multiple hormones (prolactin, ACTH, FSH, βHCG, IGF-1, TSH and calcitonin) were found in one patient with falsely elevated PTH [8], while there were three cases of a coexisting spuriously high thyroglobulin level [11]. Prior drug therapy resulting in HAMA was implicated in five patients with a falsely elevated PTH. Two had a renal transplant and had received muromonab-CD3 (a murine monoclonal antibody) [5, 6], and three were treated with a natural killer (NK) therapy with exposure to the mouse antibody (NKp46) [11].

Parathyroid disease was present in five patients with falsely high PTH. Two had secondary hyperparathyroidism due to previous renal failure. In one, there was no decline in PTH after remedial parathyroidectomy though levels were normal after removing HAMA [6], while in the other PTH reduced from 3748 to 552 pg/ml on correction [5]. Extremely high PTH (> 2500 pg/ml) in one patient also did not completely correct due to underlying secondary hyperparathyroidism [19]. There was also failure of normalisation of PTH after parathyroidectomy in a case of proven primary hyperparathyroidism which was accounted for by assay interference [9], possibly resulting from monoclonal gammopathy. Finally, in a patient with idiopathic hypoparathyroidism with undetectable levels, a subsequent spuriously high PTH (636 pg/ml) was due to HAAA [3].

Only two cases of macro-PTH are reported where respective levels were 253 and 1846 pg/ml [15, 17]. This occurs when human immunoglobulin or unknown components bind

Table 2 Case reports of falsely elevated PTH

Cases	Age	Sex	PTH (pg/ml)	Assay	Reason	Confirmation
Heterophile or human anti-animal/other antibodies						
Kasono al. (1991) [3]	73	-	636	-	HAAA;unspecified IgG	Gel filtration, AC
Cavaco et al. (1999) [4]	41	F	259	Cisbio (ELSA PTH)	HAAA	Gel filtration, AC
	39	F	230			
Cavalier et al. (2009) [5]	61	M	3748	Roche Elecsys	HAMA*	HBT, DA
Levin et al. (2011) [6]	36	F	3374	Roche	HAMA*	HBT, DA
Tanriover et al. (2012) [7]	69	F	> 2500	Siemens Healthcare Immulite 2000	MGUS	SD, DA, PEG
Gulbahar et al. (2015) [8]	33	F	566	Abbott	HAMA, RF	SD, PEG, HBT
			180	Siemens Advia Centaur XP		
van der Doelen et al. (2018) [9]	72	M	1056	Abbot Architect	HAMA, MGUS	PEG, HBT, DA
Laudes et al. (2019) [10]	36	F	> 5000	Roche Elecsys	HAMA	HBT, DA
Kim et al. (2020) [11]	40 s	M	1649	Roche Elecsys	HAMA*	HBT
	50 s	F	4667			
	60 s	F	429			
Zanchetta et al. (2021) [12]	59	F	482	Roche Elecsys	Heterophile	SD, PEG
Hassan et al. (2022) [13]	74	F	110	-	Heterophile or HAAA	DA
Calabro et al. (2022) [14]	66	M	338	Beckman Coulter Dxl 800	Heterophile	SD, HBT
Other causes						
Prodan et al. (2016) [15]	56	F	1846	Roche and Abbot	Macro PTH	SD, PEG
Neves et al. (2022) [16]	55	F	1900	-	Biotin	Biotin stopped
Cetani et al. (2023) [17]	59	M	253	-	Macro PTH	SD, PEG

PTH values rounded to nearest whole number and converted to pg/ml using UnitsLab.com

F female, *M* male, *AC* affinity chromatography, *SD* serial dilution for linearity, *PEG* polyethylene glycol precipitation (PEG) test, *HBT* heterophile blocking tube, *DA* different assay, *HAMA* human anti-mouse antibody, *HAAA* human anti-animal antibody, *MGUS* monoclonal gammopathy of undetermined significance, *RF* rheumatoid factor

*antibody induced by drug

-data not available

to PTH to form a macro-hormone complex that is metabolically inactive, cannot be excreted by the kidneys and is measured by the assay [9]. While commonly seen with prolactin (9–42%), it is very infrequent with other hormones [17]. As the falsely high PTH is not due to assay interference, in these cases, using different platforms does not significantly change the result [15].

Finally, one patient had spuriously elevated PTH (1900 pg/ml) that was attributed to a high biotin (vitamin B7) intake of 2500 mcg/day that resolved after stopping supplements [16]. This was well above the recommended intake of 30 mcg per day [2, 16] and may cause interference with assays via biotinylated capture antibodies, though in most cases, this results in spuriously low PTH levels [2].

In summary, the finding of unexpectedly high PTH discordant with the clinical picture should raise the possibility of falsely elevated levels. No single test can accurately exclude erroneous results [18, 19]. A first step to consider would be to use PEG precipitation which removes macro-PTH and in the majority of cases interfering antibodies [18]. However, there are no diagnostic cut-offs for post-precipitation recoveries. Typically, a recovery rate of 40% is used for macro-prolactinaemia [8]. In our patient and in other cases, recovery ranged from < 1.4 to 13.5% [8, 10, 12] with assay interference to 10–20% for macro-PTH [17]. Secondly, to determine if the result could be affected by interfering antibodies, a serial dilution test should be performed which generally results in nonlinearity. However, this is not always reliable as we found in our patient and as reported elsewhere [18]. Thirdly, heterophile blocking tubes or addition of animal sera can be used to remove interfering antibodies though this was not available at our laboratory. Finally, doing a repeat test on a different assay (using other animal antibodies or with blocking agents) can confirm assay interference. Notably, the PTH result can also remain high using other platforms [5], reflecting the cross-reactivity of human antibodies.

A potential implication of falsely elevated PTH in normocalcaemic patients is the erroneous diagnosis of normocalcaemic primary hyperparathyroidism (NPHT). In a recent review, Shaker et al. advise that when NPHT is suspected, PTH should be tested on two different assays [1]. Of interest, Hassan et al. found in a normocalcaemic patient a PTH of 110 pg/ml, which was 56 pg/ml when retested on a different

platform and was attributed to heterophile antibodies [13]. Importantly, in these and other cases, falsely elevated PTH levels resulted in unnecessary investigations and even surgery [2, 11, 16]. To conclude, PTH values discordant with the clinical picture (even in patients with parathyroid disease) should alert physicians to the possibility of erroneously high levels due to assay interference or macro-PTH. Good communication with testing laboratory to identify and investigate such cases is crucial.

Declarations

Conflicts of interest None.

References

1. Shaker JL, Wermers RA (2023) The eucalcemic patient with elevated parathyroid hormone levels. J Endocr Soc. https://doi.org/10.1210/jendso/bvad013/7005424
2. Cheng J, Mu D, Wang D, Qiu L, Cheng X (2023) Preanalytical considerations in parathyroid hormone measurement. Clin Chim Acta 539:259–265
3. Kasono K, Sato K, Suzuki T, Ohmura E, Demura R, Shizume K, Tsushima T, Demura H (1991) Falsely elevated serum parathyroid hormone levels due to immunoglobulin G in a patient with idiopathic hypoparathyroidism. J Clin Endocrinol Metab 72:217–222
4. Cavaco B, Leite V, Loureiro MM, Ferreira MF, Pereira MC, Santos MA, Sobrinho LG (1999) Spontaneously occurring anti-PTH autoantibodies must be considered in the differential diagnosis of patients with elevated serum PTH levels. J Endocrinol Invest 22:829–834
5. Cavalier E, Carlisi A, Chapelle JP, Orfanos P, Uzan M, Falque V, Delanaye P, Hachicha M (2009) Human anti-mouse antibodies interferences in Elecsys PTH assay after OKT3 treatment. Transplantation 87:451–452
6. Levin O, Morris LF, Wah DT, Butch AW, Yeh MW (2011) Falsely elevated plasma parathyroid hormone level mimicking tertiary hyperparathyroidism. Endocr Pract. https://doi.org/10.4158/EP10235.CR
7. Tanriover MD, Portakal O, Hapa A, Tekinel Y, Dagdelen S, Buyukasik Y, Arici M (2012) Extremely high parathyroid hormone concentrations associated with pityriasis rubra pilaris and monoclonal gammopathy of unknown significance: a clinical dilemma. Bone 51:847–850
8. Gulbahar O, Degertekin CK, Akturk M, Yalcin MM, Kalan I, Atikeler GF, Altinova AE, Yetkin I, Arslan M, Toruner F (2015) A case with immunoassay interferences in the measurement of multiple hormones. J Clin Endocrinol Metab 100:2147–2153
9. van der Doelen RHA, Nijhuis P, van der Velde R, Janssen MJW (2018) Normocalcemia but still elevated parathyroid hormone levels after parathyroidectomy. Clin Case Rep 6:1577
10. Laudes M, Frohnert J, Ivanova K, Wandinger KP (2019) PTH immunoassay interference due to human anti-mouse antibodies in a subject with obesity with normal parathyroid function. J Clin Endocrinol Metab 104:5840–5842
11. Kim D, Hong N, Cho Y, Lee SG, Rhee Y (2020) Heterophile antibody interference associated with natural killer cell therapy. Endocr J 67:1187–1192
12. Zanchetta MB, Giacoia E, Jerkovich F, Fradinger E (2021) Asymptomatic elevated parathyroid hormone level due to immunoassay interference. Osteoporos Int 32:2111–2114
13. Hassaan PM, Abouglila K, Kirty K, Tang L (2022) High Parathyroid hormone- Think out of the box! Endocr Abstr. https://doi.org/10.1530/ENDOABS.86.P187
14. Calabrò V, Lovriha S, Zandonà L, Sirianni F, Fabris B, Bernardi S (2022) A case report of PTH elevation due to immunoassay interference. J Endocrinol Invest 45:2201–2202
15. Prodan P, Nandoshvili E, Webster C, Shakher J (2016) Asymptomatic elevated PTH level due to immunoassay interference resulting from Macro-PTH: a case report. Endocr Abstr. https://doi.org/10.1530/ENDOABS.44.CC4
16. Neves G, Carvalho Lira E, Author C (2022) False hyperparathyroidism secondary to biotin prolonged use: a case report. Int J Nutrol. https://doi.org/10.54448/IJN22207
17. Cetani F, Centoni R, Marcocci C (2023) Macro-PTH, a rare cause of unexplained elevated serum PTH levels. J Endocrinol Invest 46:1039–1040
18. Sturgeon CM, Viljoen A (2011) Analytical error and interference in immunoassay: minimizing risk. Ann Clin Biochem 48:418–432
19. Braunstein GD (2022) Spurious serum hormone immunoassay results: causes, recognition, management. Eur Endocrinol 18:141–147
20. Cavalier E, Carlisi A, Chapelle JP, Delanaye P (2008) False positive PTH results: an easy strategy to test and detect analytical interferences in routine practice. Clin Chim Acta 387:150–152