J Musculoskelet Neuronal Interact 2019; 19(3):379-384

Journal of Musculoskeletal and Neuronal Interactions JMNI

Case Report

Lessons learned from the management of Hungry Bone Syndrome following the removal of an Atypical Parathyroid Adenoma

Dimos Florakis[1], Stavros Karakozis[2], Sophia Tseleni-Balafouta[3], Polyzois Makras[4]

[1]Department of Endocrinology, Metropolitan General Hospital, Athens, Greece; [2]Department of Endocrine Surgery, Hygeia Hospitals Group, Athens, Greece; [3]Department of Pathology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [4]Department of Endocrinology and Diabetes and Department of Medical Research, 251 Hellenic Air Force General Hospital, Athens, Greece

Abstract

Hungry Bone Syndrome (HBS) refers to rapid, profound, and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesemia occurring in patients with increased bone turnover after successful management of the underlying disorder. We describe a male patient with primary hyperparathyroidism (PHPT), in whom HBS was diagnosed 6 months after parathyroidectomy. Histopathologic examination revealed an atypical parathyroid adenoma (APA), while immunohistochemistry showed cell proliferation index Ki-67 10% and overexpression of cyclin D1 (>90%). Preoperative treatment with vitamin D3 had normalized 25OHD and alkaline phosphatase levels, reflected in an improvement in bone turnover prior to surgery. Postoperative treatment for HBS with alfacalcidol, calcium, vitamin D3 and magnesium was administered for a long period. This treatment prevented severe postoperative hypocalcemia and he was discharged two days later. Preoperative cinacalcet treatment did not reduce hypercalcemia implying that the tumor had lack of calcium-sensing receptors (CaSR). In conclusion, preoperative restoration of low 25OHD levels is essential for prevention of HBS. Postoperative treatment with active metabolites of vitamin D must be initiated as early as possible, in order to prevent or minimize the development of HBS, and to reduce the duration of hospitalization.

Keywords: Hungry Bone Syndrome, Atypical Parathyroid Adenoma, Ki-67 Index, Vitamin D3, Alfacalcidol

Introduction

Hungry Bone Syndrome (HBS) is usually a complication of successful parathyroidectomy for severe primary hyperparathyroidism (PHPT) which is associated with preoperative high bone turnover. HBS is characterized by profound and prolonged hypocalcemia (corrected serum calcium <8.5 mg/dL), hypophosphatemia and hypomagnesemia[1]. The abrupt postoperative removal of the high circulating levels of PTH (parathyroid hormone) results in an increased influx of calcium into the skeleton in order to meet the needs of the rebound bone formation, while bone resorption is arrested. Postoperatively, HBS is characterized by elevated PTH levels in patients with severe PHPT, whereas HBS is quite rare in patients with mild PHPT[2]. The most common diagnoses associated with HBS are PHPT and secondary or tertiary hyperparathyroidism after parathyroidectomy, in patients with end-stage renal disease receiving renal replacement therapy or with a functioning renal transplant[3]. Another diagnosis sometimes associated with usually a mild form of HBS is severe thyrotoxicosis associated with high bone turnover in which hypocalcaemia may occur in up to 46% of patients, while HBS may last for up to 3 months after the initiation of hyperthyroidism treatment (surgical or medical)[4,5]. In contrast to HBS due to PHPT, hypocalcaemia that arises following treatment for hyperthyroidism is associated with appropriate increase of PTH levels[1]. Less frequent causes of HBS are parathyroid cancer (PC)[6,7] and metastatic prostate cancer[8]. Bone metastases from prostate cancer are predominantly osteoblastic and commonly cause increased levels of PTH as

The authors have no conflict of interest.

Corresponding author: Dimos Florakis MD, PhD, Ypsilantou 54, Halandri 15232, Athens, Greece
E-mail: florakid@otenet.gr

Edited by: G. Lyritis
Accepted 3 May 2019

Table 1. Laboratory findings preoperatively (**Preop**) and postoperatively (**Postop**).

	Preop	Preop cinacalcet vitamin D3 magnesium	Postop 48 h	Postop 6m vitamin D3 calcium magnesium without alfacalcidol HBS [b]	Postop 8m alfacalcidol vitamin D3 calcium magnesium	Post 20m alendronate alfacalcidol vitamin D3 calcium magnesium	Postop 4 years without treatment	Reference values
Corrected Calcium serum [a]	12.26	12.36	8.64	8.06	9.04	8.94	8.76	8.6 - 10.2
Calcium serum (mg/dL)	12.5	12.6	8.8	8.3	9.2	9.1	9.0	8.6 - 10.2
Albumin serum (mg/dL)	4.3	4.3	4.2	4.3	4.2	4.2	4.3	3.5 - 5.5
Phosphate serum (mg/dL)	1.9	1.6	3.6	2.4	2.7	3.2	1.8	2.5 - 4.5
Magnesium serum (mg/dL)	1.7			1.8			1.8	1.6 - 2.6
Creatinine serum (mg/dL)	0.9			1.0			1.0	0.4 - 1.09
Alkaline phosphatase (ALP) (U/L)	1015	275		123		68	73	50 - 290
24-hour urine calcium (mg/24h)	485			37	218		208	100 - 300
24-hour urine creatinine (mg/24h)	1356				1655		1645	1040- 2300
25OHD (ng/mL)	8	27		31			15.2	> 20 ng/mL
1,25 $(OH)_2$ D (pg/mL)	18				25		26.3	18 - 65
PTH (pg/mL)	1131	1315	34	120	60	62	102	15 - 65
TSH (μUI/mL)	1.87			2.6				0.36 - 4.94

[a] ***Corrected calcium*** *with albumin using the following formula: calcium measured + 0.8 (4 - albumin measured).*
[b] ***HBS****: Hungry bone syndrome.*

calcium is transferred from serum into the osteoblast-rich neoplastic environment[8].

Nowadays, HBS rarely involves skeletal manifestations such as brown tumors and osteitis fibrosa cystica, whereas fragility fractures due to severe osteoporosis are more likely to be occurred. HBS develops postoperatively in up to 13% of patients with PHPT, although this figure varies among centers[1].

The duration of the syndrome has been defined as the time needed for bone remineralization and normalization of bone turnover markers, as well as the time required for normalization of serum calcium following successful parathyroidectomy[1]. In addition, improvement or normalization of bone mineral density (BMD) is considered to be a criterion for resolution of HBS[9], and several studies adopting this notion have reported that HBS may last from 4.5 to 16 months[9]. Nevertheless, there is as yet no consensus on a definition of disease duration for HBS.

We herein describe a case of PHPT without severe skeletal findings, in which HBS was diagnosed 6 months after the surgical excision of an atypical parathyroid adenoma (APA).

Table 2. Dual energy X-ray absorptiometry (DXA) values preoperatively and postoperatively.

	Preoperative	Postoperative 12m [a]	Postoperative 36m
Left Femoral Neck			
BMD (g/cm^2)	0.443	0.706	0.746
Z-score	- 4.28	- 2.3	- 1.9
Right Femoral Neck			
BMD (g/cm^2)	n/a	0.773	0.812
Z-score		- 1.8	- 1.4
Lumbar L1-L4			
BMD (g/cm^2)	n/a	1.059	1.116
Z-score		- 1.3	- 0.8

Osteoporosis is diagnosed when BMD is below the expected range for age (Z-score < -2.0)
[a] Treatment with alendronate was given for 1 year after postoperative DXA at 12 months

Case presentation

A 44-year-old Caucasian male presented with a history of arthralgia and myalgia for several months. Medical history of nephrolithiasis was reported.

The initial laboratory results were as follows: corrected serum calcium 12.26 mg/dL (normal range 8.6-10.2), phosphate levels 1.9 mg/dL (normal range 2.5-4.5), magnesium levels 1.7 mg/dL (normal range 1.6-2.6) and alkaline phosphatase levels (ALP) 1015 U/L (normal range 50-290). The elevated PTH levels of 1131 pg/mL (normal range 15-65) together with hypercalcaemia confirmed the diagnosis of PHPT, despite low levels of 25OHD and 1,25(OH)$_2$D of 8 ng/mL (sufficiency >20) and 18 pg/mL (normal range 18-65), respectively. Hypercalciuria (485 mg/24 hours) was also found (Table 1).

Skeletal X-rays of the hip-pelvis and lumbar spine showed diffuse osteopenia without any skeletal fractures. The initial dual energy X-ray absorptiometry (DXA) scan confirmed BMD below the expected range for age[10] [left neck Z-score -4.28] (Table 2). Technetium-99m-pertechnetate whole-body scan did not reveal any skeletal lesion.

Neck ultrasonography showed a hypoechogenic mass measuring 2.6 x 3.6 cm with a well-defined margin posterior to the right lobe of the thyroid gland, without signs of blood flow (Figure 1 a, b). ^{99}Tc-sestamibi scintigraphy revealed persistence of the radionucleotide in the right posterior parathyroid gland, but with extension of the radionucleotide to the upper right mediastinum (Figure 1c). Therefore, neck MRI was performed and a large mass with cystic degeneration measuring 8.7 x 4.6 cm was found posterior to the right thyroid lobe extending to the right mediastinum, while shifting the trachea and the esophagus to the left (Figure 1d).

A diagnosis of PHPT due to a large parathyroid tumor was established. Preoperative treatment with cinacalcet 30 mg b.i.d. was initiated with a daily dose of 2000 IU vitamin D3 (cholecalciferol) and 243 mg of magnesium, in order to control the hypercalcemia and correct the low levels of 25OHD and magnesium, respectively. Nevertheless, corrected serum calcium levels remained increased at 12.36 mg/dL, while 25OHD levels were partially corrected to 15 ng/mL. Daily doses of cinacalcet and vitamin D3 were subsequently increased to 60 mg t.i.d. and 4000 IU, respectively, resulting in correction of 25OHD and ALP levels, although hypercalcemia persisted (Table 1). Subsequently, cinacalcet treatment was ceased due to the unresolved hypercalcaemia, while the vitamin D3 daily dose was reduced to 2000 IU, since 25OHD levels had increased to 27 ng/mL. Bisphosphonates were not used preoperatively.

Total surgical excision of the tumor was performed without any surgical complications. Postoperatively the patient had asymptomatic hypocalcaemia (corrected serum calcium 7.34 mg/dL) with inappropriately normal PTH levels of 34 pg/ml, confirming successful parathyroidectomy (Table 1). Alfacalcidol 1mcg and calcium carbonate 4 gr daily were initiated with concomitant use of 1600 IU vitamin D$_3$ and 243 mg magnesium. The patient was discharged two days after surgery with corrected serum calcium concentration at 8.64 mg/dl, while calcium carbonate dose was reduced to 2 grams.

Histopathological examination revealed a tumor weighing 22 grams and measuring 7.2 x 4.5 x 2.7 cm. The parathyroid neoplasm consisted of solid and cystic areas with fibrosis and partial capsular invasion, however, without extensive local infiltration or metastasis. Immunohistochemistry showed increased expression of cyclin D1 (>90%) and cell proliferation Ki-67 index (with MIB 1 antibody) was 10%. The tumor was classified as an APA[11] (Figure 1 e, f).

Six months later, PTH levels were increased with low levels of calcium, phosphate and magnesium, and normal levels of 25OHD and ALP (Table 1). The patient's treatment included calcium carbonate/D3 tablets of 1000mg/880 IU twice per day and 243 mg of magnesium, whereas alfacalcidol had

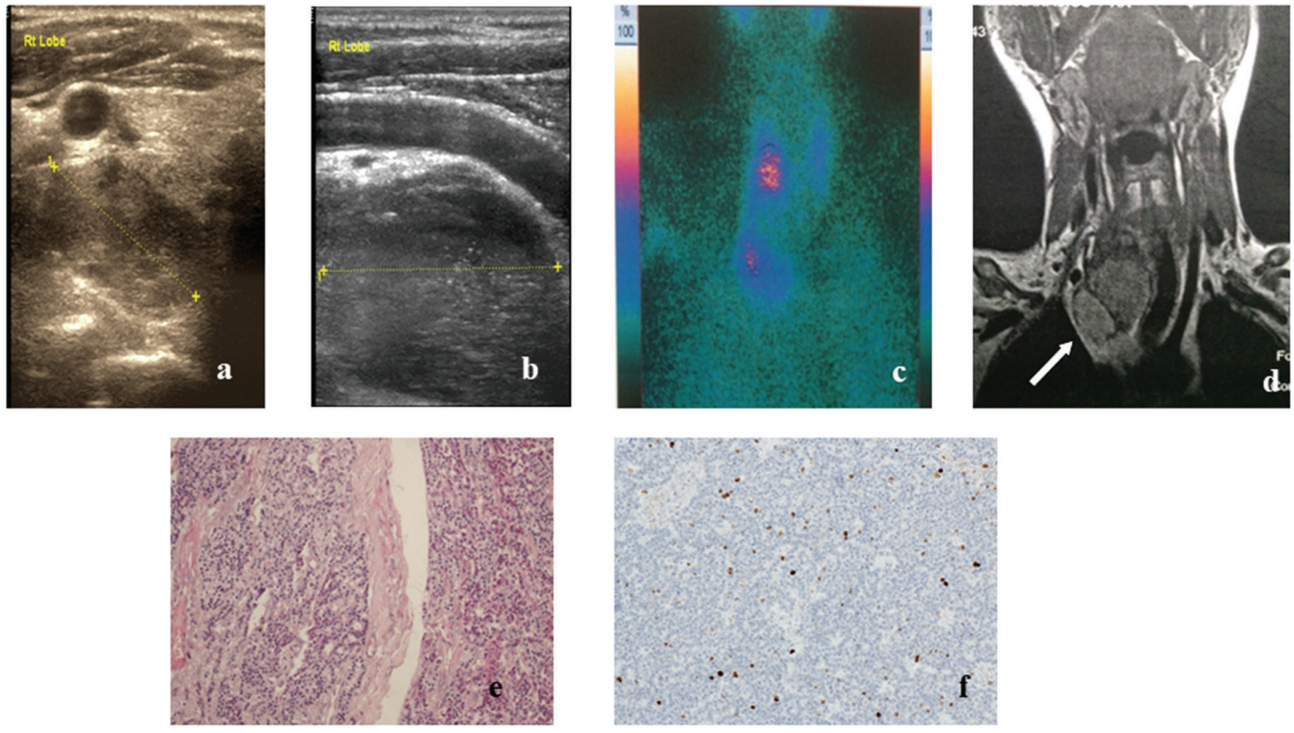

Figure 1. Neck ultrasonoraphy (a, b): Hypoechogenic mass measuring 2.6 x 3.6 cm with well-defined margin posterior to the right lobe of the thyroid gland without signs of blood flow. 99Tc-sestamibi scintigraphy (c): Persistence of the radionuclide material in the right posterior parathyroid gland with extension of the radionuclide material in the upper right mediastinum. Neck MRI (d): A large mass with cystic degeneration measuring 8.7 x 4.6 cm posterior to the right thyroid lobe extending to the right mediastinum with trachea and esophagus shift to the left. (e): Atypical parathyroid adenoma. HE 250X. (f): Overexpression of the proliferation index Ki67 (MIB 1). Immunohistochemistry 250X.

been ceased 2 months previously. HBS was diagnosed and alfacalcidol 1mcg was recommended, with concomitant use of calcium carbonate/D3 and magnesium. PTH and calcium levels were normalized, after 2 months (Table 1).

Twelve months following parathyroidectomy, DXA showed a significant increase of 59.4% in the left femoral neck BMD (Table 2). As BMD, in the left femoral neck, was still below the expected range for age [left neck Z-score -2.3], alendronate 70 mg weekly was administered for 12 months as additional treatment together with alfacalcidol, calcium carbonate, cholecalciferol, and magnesium. Six months later, serum levels of corrected calcium, phosphate, ALP and PTH were normalized (Table 1). Three years after parathyroidectomy, a new DXA showed a further increase of BMD in all skeletal sites: lumbar spine (+5.4%); left hip (+5.7%) and of the right hip (+5.0%), indicating a positive effect of alendronate treatment and parathyroidectomy (Table 2). It was therefore decided that no additional treatment was required.

Six months later (4 years postoperatively), PTH was once again increased to 102 pg/mL with low levels of phosphate, magnesium, and 25OHD, while corrected calcium levels were low normal at 8.76 mg/dL (Table 1).

Secondary hyperparathyroidism (sHPT) due to vitamin D deficiency seemed as the most possible diagnosis, although persistent of HBS was a less likely option, and treatment with alfacalcidol, calcium, vitamin D3 and magnesium was recommended. Additional treatment with alendronate was not considered necessary as BMD values were within the expected range for age (Table 2).

Discussion

Hypocalcemia following successful parathyroidectomy is usually transient, lasting less than a week, since the associated PHPT bone disease is frequently mild and the remaining normal parathyroid glands recover rapidly, even after long-term suppression by the hyperfunctioning parathyroid adenoma[12,13].

In patients with PHPT and preoperative high rates of bone turnover, a successful parathyroidectomy limits osteoclastic resorption, which in turn decreases the activation frequency of new remodeling sites and remodeling space, leading to a consequent gain of bone mass. This mechanism in combination with the homeostatic increase of bone formation which corrects the PHPT-induced bone

deficits, is believed to be the etiology of the rapid, severe and prolonged hypocalcemia that occurs in HBS[1]. In addition, hypophosphataemia in HBS is probably due to an increase in bone uptake that facilitates matrix remineralization[14,15]. Magnesium levels after parathyroidectomy may decrease secondary to increased bone mineralization, especially in patients with PTH-related bone disease, such as osteitis fibrosa[16]. In our case, magnesium level was low normal preoperatively and remained low normal postoperatively, despite supplementation for a long period. Hypomagnesemia in PHPT is an uncommon finding. It has been shown that few patients with PHPT have high urinary magnesium output, indicating a defect in renal magnesium retention[16].

PHPT-related bone disease, such as brown tumors or osteitis fibrosa and skeletal fractures, is of considerable importance for the development of HBS, as it has been reported in 25-90% of patients with skeletal involvement compared with 0-6% of patients without skeletal involvement[1]. It is of interest that our patient developed HBS without any of the above skeletal findings or fracture. Another interesting point is the young age of our patient, since older age at the time of HBS diagnosis is considered as an additional risk factor for the development of the syndrome[1].

Low preoperative 25OHD has been also proposed as an important factor that increases the risk for HBS[2]. In PHPT, vitamin D insufficiency is more common than in the general population[2]. Low 25OHD levels in PHPT patients, have been associated with greater severity of disease, higher bone turnover and BMD reduction, more severe postoperative hypocalcemia, and higher overall PTH levels[2]. A randomized study, showed that daily high-dose vitamin D supplementation of 2800 IU for 6 months preoperatively and 6 months postoperatively is a safe way to improves vitamin D status in PHPT patients, without increasing plasma or urinary calcium[2]. In addition, preoperative treatment with vitamin D3 reduced bone resorption and was followed by postoperative reduction of PTH and ALP levels, confirming that preoperative vitamin D3 supplementation may decrease the likelihood of development of HBS[2]. In our case, the preoperative vitamin D3 treatment normalized 25OHD and ALP levels, reflecting a possible improvement of bone turnover prior to surgery. Treatment with alfacalcidol and calcium was initiated immediately after parathyroidectomy, with concomitant use of cholecalciferol and magnesium. This treatment course prevented severe postoperative hypocalcemia, and the patient was discharged two days later, without the need for an intravenous calcium infusion. A case report has been published with a patient presenting protracted and severe HBS requiring 3 months of intravenous calcium supplementation, whereas the patient received ergocalciferol and calcitriol, before and after parathyroidectomy[9]. The authors reported that 25OHD levels never reached a value above 30 ng/ml, despite the administration of ergocalciferol, and this underlines the importance of 25OHD levels normalization with cholecalciferol.

Postoperative treatment with active metabolites of vitamin D with concomitant use of calcium and cholecalciferol are considered mandatory and need to be initiated as early possible in order to prevent or ameliorate HBS. Several case reports of patients with HBS have described the difficulties involved in the postoperative management of hypocalcemia whenever the treatment consists solely of calcium plus ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) without concomitant use of vitamin D active metabolites[6,9].

In our case, the preoperative hypercalcemia was not adequately controlled even with high-dose cinacalcet treatment, this arousing speculation that the tumor lacked expression of the calcium sensing receptor (CaSR). Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the CaSR to extracellular calcium. Immunohistochemical studies have shown that global loss of CaSR staining in parathyroid tumors is a diagnostic marker for PC[17]. However, in our case study the histopathologic diagnosis of an APA was established, because the tumor exhibited some features of a parathyroid carcinoma such as fibrosis and partial capsular invasion but had lack of unequivocal invasive growth and metastasis. APA may be considered tumor of uncertain malignant potential, and most patients with APA have a benign clinical course[11].

Most of the bone loss in PHPT patients is reversible after parathyroidectomy. In a case series of patients with HBS, parathyroidectomy improved femoral neck BMD scores from 35% to 131% 1 year after successful surgery. In addition, case reports showed an increase in BMD of the lumbar spine of 27% to 63% 1 year after parathyroidectomy[1].

Preoperative treatment with bisphosphonates in HBS is controversial. A retrospective case series of 46 patients with severe bone disease, who were treated with zoledronate preoperatively, showed a low frequency of postoperative HBS of only 4%[18]. In contrast, other case reports using bisphosphonates prior to surgery demonstrated no such effect[19]. The aim of the preoperative bisphosphonate treatment is to reduce bone turnover by inhibition of osteoclast bone resorption, and to decrease the activation frequency of remodeling space, thus resulting in refilling of remodeling space and increasing mineralization of the bone. However, short-term preoperative bisphosphonate treatment may exacerbate postoperative hypocalcemia by reducing bone resorption, without allowing time for a coupled decrease in bone formation. In our case, alendronate was given for 1 year, postoperatively, when the DXA has showed that BMD was still below the expected range for age.

In our patient high PTH levels with low normal calcium, phosphate, and suboptimal 25OHD levels were measured 4 years after parathyroidectomy, concomitantly with normal BMD, ALP, and 24-hour urine calcium levels (Table 1). Postoperative treatment included alendronate for 1 year and cholecalciferol, alfacalcidol and magnesium for more than 3 years. Secondary hyperparathyroidism (sHPT) due to vitamin D deficiency may be considered as the most likely diagnosis in our case. However, in sHPT the increases of serum PTH associated with vitamin D deficiency are usually within the high normal reference range[20]. In a large vitamin D study, it was determined that the negative relationship between

serum PTH and serum 25(OH)D was significant only when serum 25(OH)D was lower than 12 ng/ml[21]. Furthermore, high PTH levels occurs in only 10% to 33% of people with vitamin D insufficiency[22]. In our case report, the high PTH levels in correlation with the lack of hypocalcemia and the normal 24-hour urine calcium levels indicate that HBS could be an alternative, less possible, diagnosis. Unfortunately, there are no available data regarding the postoperative use of bisphosphonates after parathyroidectomy, for the prevention or amelioration of HBS. However, it may be speculated that the postoperative treatment with alendronate for 1 year maintained low normal calcium levels by decreasing calcium influx to the bone, and thus masking the presentation of HBS while making sHPT the most acceptable diagnosis in our case.

Conclusion

Preoperative restoration of 25OHD levels is essential for prevention of HBS, though only vitamin D3 preparations are recommended, since vitamin D2 preparations have much lower efficiency in restoring vitamin D levels[23]. Postoperative treatment with active metabolites of vitamin D, must be initiated as early as possible in order to prevent the development of HBS, and to reduce the duration of hospitalization. Magnesium supplementation is also important for the prevention and treatment of HBS, given that hypocalcemia is very difficult to resolve if there is concomitant hypomagnesemia. Data on the management of HBS are limited, while clinical guidelines and consensus regarding the precise definition and management of the syndrome are as yet lacking.

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