Hungry bone syndrome - a foreseen complication: theory versus practice

Amalia Ioana Arhire*[,1], Cristina Stefan[1,2], Suzana Florea[3], Simona Tau[1], Carmen Gabriela Barbu[1,4]

[1]Endocrinology Department, Elias Hospital, Bucharest, Romania, [2]Ghencea Medical Center, Bucharest, Romania, [3]Internal Medicine Department, Elias Hospital, Bucharest, Romania [4]"Carol Davila" University of Medicine and Pharmacy Bucharest, Romania,

Abstract

Hungry bone syndrome represents a severe and rapid hypocalcemia associated with hypophosphatemia and hypomagnesaemia, which remain a challenge in the post-operative management of primary hyperparathyroidism (PHPT). We present a case of hungry bone syndrome which turned out to be atypical in spite of the appropriate prevention and treatment management because of a neglected primary hyperparathyroidism that was associated with iron-deficiency, megaloblastic anemia and bone fibrosis. Moreover, the renal failure suggests that the severity of disease was determined by the period of hyperparathyroidism and the increased number of complications.

Keywords: *primary hyperparathyroidism, hungry bone syndrome, hypocalcemia, anemia, severe osteoporosis*

Introduction

Hungry bone syndrome (HBS) refers to a severe, rapid and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesaemia that are the consequences of suppressed parathyroid hormone levels at patients with prior high bone turnover [1-6, 9, 11, 12]. Various risk factors have been suggested for the development of this syndrome, including old age, the long term of primary hyperparathyroidism, the dimensions of the parathyroid glands, radiological signs of active bone disease and low vitamin D levels. After parathyroidectomy, rapid decrease of serum calcium levels occurs, as a sign of successfully removing of one or more hyperactive parathyroid adenoma [1, 4, 6, 9, 11, 12, 14].

Based on a systemic review of the literature made by JE Witteveen the term 'hungry bone syndrome' has been linked to the severe (serum calcium < 8 mg/dl) and prolonged (longer than 4 days post-surgery hypocalcemia), in the case of a curative treatment (parathyroidectomy) of severe hyperparathyroidism. This hypocalcemia is the result of the rapid influx of calcium into the bone as the resorption effect of circulating PTH is abolished and the bone formation is pursued and improved. [1]

Although there are suggestions that preoperative treatment with bisphosphonates may reduce post-operative hypocalcemia and make it more manageable, it is not always indicated in practice [1, 4, 5, 9, 10].

We present a case of a foreseen hungry bone syndrome which turned out to be severe and atypical in spite of the administration of IV bisphosphonates prior to the surgery and the

Received: October 2015; Accepted after review: December 2015; Published: December 2015.

*Corresponding author: Amalia Ioana Arhire, MD, Endocrinology Department, Elias Hospital, 17 Marasti Boulevard, sector 1, 011461, Bucharest, Romania. Tel: 0040 21 316 16 00.
E-mail: drarhireamalia@yahoo.com

important substitution doses of calcium and vitamin D [1, 3, 10].

Case report

A 66-year- old female with severe osteoporosis, multiple fractures and chronic renal disease was admitted in the Endocrinology Department at the Elias Hospital for the management of a severe hypercalcemia (14.6 mg/dl). From the case history we mention that the patient was diagnosed with severe osteoporosis. A CT scan performed in 2014 found pubis (Figure 1) and ischium fractures, two osteolytic lesions, one on the right acetabulum and one on first sacrum vertebra (Figure 2).

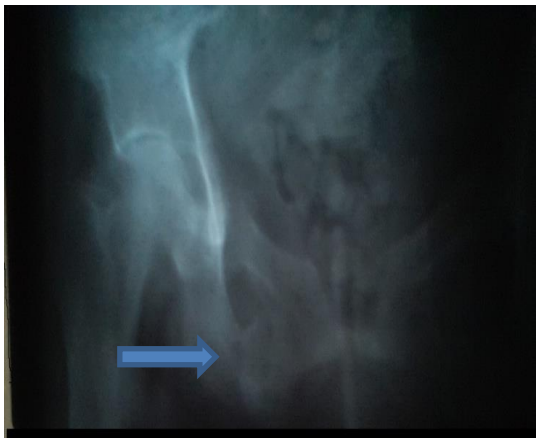

Fig. 1. Pubis fracture

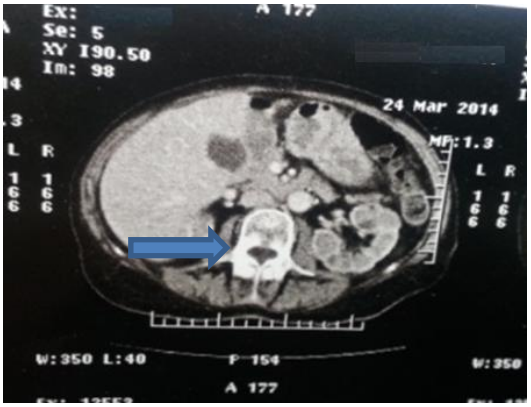

Fig. 2. Osteolytic lesion on the S1 vertebra

The DXA showed a total hip T score of -3DS, a lumbar T score of -1.8DS and -4.4 DS on the forearm bones.

The laboratory investigation showed hypercalcemia associated with high PTH levels (4000 pg/ml), elevated total alkaline phosphatase (636 UI/L), low serum phosphorus level (2.5 mg/dl), creatinine clearance of 57 ml/mn, microcytic hypochromic anemia, proteinuria, high calciuria (638.4 mg/24h). The value of 25(OH)-vitamin D was low (10.2 ng/ml), suggesting the prolonged term of primary hyperparathyroidism [1, 9, 16]. The thyroid function was normal with a TSH of 1.86mUI/dl, the anti-thyroglobulin and anti-thyroperoxidase antibodies were negative. The thyroid ultrasonography revealed a multi micronodular goiter and a hypoechoic mass, posterior of the left thyroid lobe with dimensions of 2.4/1.5 cm, compatible with an abnormal parathyroid gland. Considering the dimensions of the parathyroid adenoma, the fact that it was unique and the high serum calcium, the parathyroid scintigraphy was not performed. Subsequently, we established the diagnosis: primary hyperparathyroidism caused by a parathyroid adenoma associated with euthyroid multinodular goiter and surgical treatment was recommended. Parathyroidectomy (removing a 2.4/1.5 cm adenoma) (Figure 3), and a subtotal thyroidectomy for the multinodular goiter were performed.

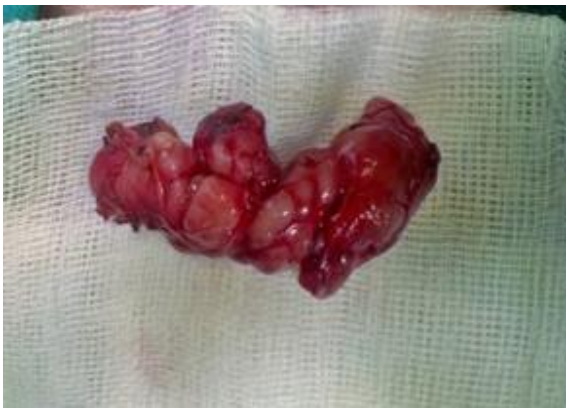

Fig. 3. Parathyroid adenoma – resection piece

Considering the extremely high PTH values parathyroid carcinoma was suspected, but the histological examination found an encapsulated, cellular, homogenous lesion, composed of chief cells with some oxyphil cells in a delicate capillary network, with minimal mitotic activity. There was no capsular, vascular of adjacent tissue invasion, pleading for a benign adenoma.

Initially, the clinical outcome was favorable under calcium and vitamin D supplements administration, but after 6 days the patient presented in the Emergency Room for severe paresthesia of the limbs and hypocalcemia (6.4 mg/dl) despite the daily treatment with 1.8 g of calcium, 1200 UI of cholecalciferol and 1.5 µg of alphacalcidol (Figure 4).

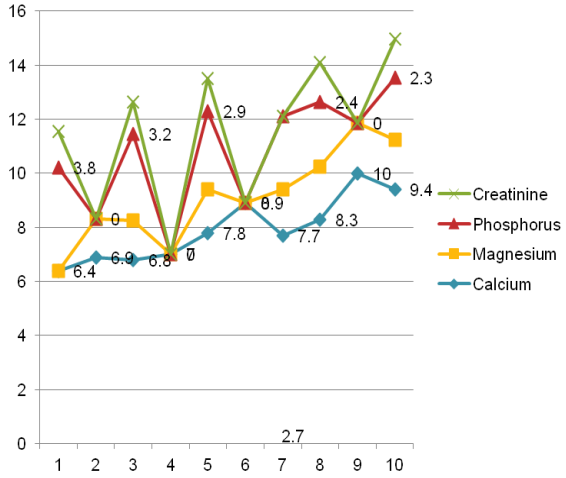

Fig. 4. Evolution under treatment

The clinical examination revealed severe paresthesia and muscle aches, slightly dehydrated and pail skin, bilateral and multiple lipoma on the forearms (Figure 5), hip arthralgia with irradiation in the limb, blood pressure of 110/80 mmHg, heart rate of 90bpm, constipation, left cecity.

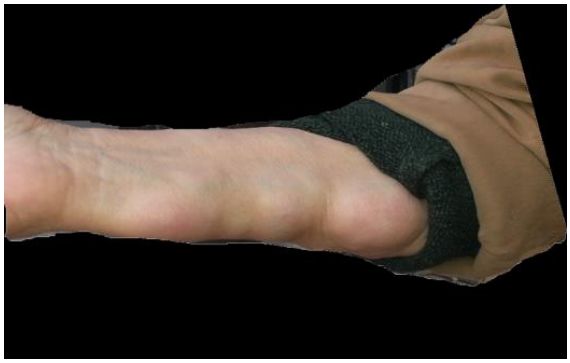

Fig. 5. Multiple bilateral lipoma of the forearm

Biologically, hypocalcaemia (6.4 mg/dl), high PTH levels (80.1 pg/dl), moderate normocytic normochromic anemia, creatinine clearance of 32ml/min and inflammatory syndrome with an ESR of 77 mm/h (Table 1) were identified.

In order to alleviate the clinical manifestations and reach a normal total calcaemia, continuous intravenous administration of calcium was needed, with a gradual dose increase to a total dose of 14 g per day, for three days, associated with oral vitamin D up to 6 µg/day and magnesium administration.

Afterwards, we replaced the intravenous calcium with oral supplementation. For the aggravated anemia, a hematological consult was required, setting the diagnosis of iron-deficiency anemia and the patient received 1 unit of blood. After blood transfusion, hemoglobin was at the same level, so a medullar aspirate was performed which raised the suspicion of iron-deficiency and megaloblastic anemia. Bone biopsy was performed, showing bone fibrosis and hipocellularity of the bone marrow.

The clinical outcome of the patient was favorable, after 3 months the serum calcium level was normal (9.3 mg/dl) due to daily treatment with 0.5 mcg of alphacalcidol and 2000mg calcium (Table 2).

Also the anemia was improved with hemoglobin level reaching 10.5 mg/dl (Figure 6).

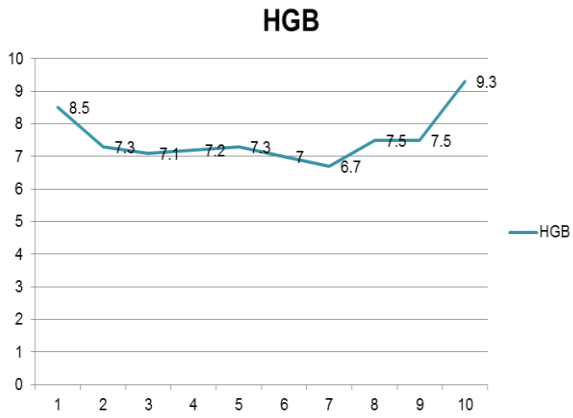

Fig. 6. Evolution of anemia

The PTH was normal (20 pg./ml). Another osteodensitometry was scheduled in 6 months.

Table 1. Biological investigations
(ALKP – alkaline phosphatase, iPTH – intact PTH, MDRD – Modification of Diet in Renal Disease)

Blood test	**Value** (normal values)
Total serum Ca	6.4 mg/dl (8.5-10.2)
Total serum proteins	6.2g/dl(6.6-8.7)
HGB	8.5 g/dl(12-15.2)
Creatinine	1.35mg/dl (0.5-1.4)
Urea	73.5mg/dl (10-20)
MDRD	32ml/min/1.73m2
ESR	75mm mm/h (6-13)
Phosphorus	3.8mg/dl(2.7-4.5)
Magnesium	3.8mg/dl (1.58-2.55)
Total ALKP	1928U/L (44-147)
iPTH	80 pg/ml (15-65)
25 OH vitamin D	10.2 ng/ml (>30)

Table 2. Management of hungry bone syndrome

Calcium	6.4	6.9	6.8	7	7.8	8.9	8.3	10
Magnesium		1.41	1.46		1.6		1.94	1.87
Phosphorus	3.8		3.2		2.9		2.4	
Creatinine	1.35		1.17		1.22		1.45	
ALKP	1928		1749		1661			
iPTH	80.1							
Dose of orl calcium	1.8g	4g	3.2g	1.2g	1.2g	1.2g	3.2g	6.2g
Dose of calcium iv		30mg	80mg	120mg	120mg	120mg		
Dose of vitaminD	1200,0.5ug	3520UI,4ug	1500UI, 4ug	300UI,6ug	300UI,6ug	300UI,6ug	300UI,6ug	4700UI,3ug
Dose of magnesium			450mg	450mg	450mg	450mg	450mg	450mg

Discussions

The association between renal impairment, low 25(OH)-vitamin D, anemia, marrow fibrosis, severe osteoporosis, fibro-cystic osteitis, high level of alkaline phosphatase and considerable volume of the parathyroid adenoma suggested a long neglected primary hyperparathyroidism and were considerable risk factors for a post-operative hungry bone syndrome. The stage 3 chronic renal disease associated to nephrocalcinosis might be related to the forearm lipomas, a soft tissue ultrasonography might be useful to assess this condition. There are no current guidelines to manage this severe hypocalcaemia related to hungry bone syndrome, but the treatment is aimed to normalize the serum calcium and restored the physiological bone turnover using high doses of calcium, vitamin D and metabolites of vitamin D, but also magnesium [3-6].

The preferred administration for calcium is iv initially, but it is required to associate oral supplements of calcium and vitamin D with alphacalcidol or calcitriol as soon as possible. Although the level of serum calcium usually responds rapidly to this treatment, this is not always the case [1, 4, 5, 15].

Preoperative treatment of vitamin D deficiency with cholecalcipherol does not increase calciuria, the administration of iv bisphosphonates is recommended, preferring zolendronic acid to pamidronate for its effects on the calcium level [5, 10, 13, 15].

The differential diagnosis between primary and secondary hyperparathyroidism was made in our case; we note that secondary hyperparathyroidism was excluded because of the important serum hypercalcaemia (in secondary hyperparathyroidism the calcium level is normal or low), low phosphorus level, very high value of PTH. The low level of vitamin D is often seen in neglected primary

hyperparathyroidism because of the use of 1,25 - (OH) - vitamin D by PTH to absorb intestinal calcium but also to the high levels of serum calcium that directly inhibit the renal 1α-hydroxylase [1, 4, 16]. The PTH levels in secondary hyperparathyroidism are not as high.

Our first guess at the second admission of the patient was noncompliance to the treatment so she was admitted considering the symptomatic hypocalcaemia and the need for the adjustment of treatment. Reviewing the literature, we found that anemia and marrow fibrosis are often found in patients with neglected primary hyperparathyroidism and both improved after successful parathyroidectomy. The possible mechanism of PHPT causing anemia and marrow fibrosis is that PTH has a stimulatory effect on marrow fibroblasts, leading to bone marrow fibrosis, but also to the release of cytokines IL-6 and TNF-α from the osteoclasts that play an indirect role in the pathogenesis of fibrosis [7, 8, 18].

Conclusion

Hungry bone syndrome is a severe complication of neglected primary hyperparathyroidism, which associated with iron-deficiency, megaloblastic anemia and bone fibrosis, besides the renal failure, suggests that the severity was determined by the term of hyperparathyroidism and the increased number of complications. Hungry bone syndrome appeared as a rare but severe condition triggered by the cure of a long standing primary hyperparathyroidism in spite of the prophylactic treatment.

Conflict of interest – None declared.

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