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Hungry Bone Syndrome after Surgical Treatment of Hyperparathyroidism in Dialysis Patients: About Two (2) Cases in Senegal

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Abstract

***Introduction:** Hungry bone syndrome (HBS) is a complication of hyperparathyroidism surgical management characterized by deep hypocalcaemia and hypophosphatemia secondary to a massive influx of calcium to an avid bone.*

***Observations:** We report the cases of two (2) patients dialysed for chronic kidney disease (CKD) whose initial nephropathy is a hypertensive nephropathy. They posed the problem of CKD-mineral bone disorder (CKD-MBD) fibrous osteitis type with intact parathyroid hormone (PTH) up to 40N for which a subtotal parathyroidectomy (PTX) was performed with postoperative biological anomalies in favour of the diagnosis of hungry bone syndrome.*

***Conclusion:** HBS still intervenes on osteopathies of intense turnover. Its treatment is difficult, based on prolonged calcium and vitamin D supplementation. However, perioperative therapeutic protocols settlement seems essential in order to minimize the risks of its occurrence.*

Keywords: *Hungry bone syndrome – secondary hyperparathyroidism – parathyroidectomy – dialysis.*

Introduction

Among the chronic kidney disease–mineral bone disorders (CKD–MBD), the most common skeletal manifestations are secondary hyperparathyroidism (SHPT), which is characterized by an increase in osteoclastic bone resorption. SHPT is a common complication of CKD with a prevalence accounting for 30 to 50% according to the authors **[1-4].** This prevalence increases with the duration of dialysis **[2, 3].** Its treatment is primarily preventive, aimed at correcting hypocalcaemia and hypophosphatemia to reduce the parathyroid response and especially to prevent complications. Medical treatment consists of calcium and vitamin D supplementation, phosphorus chelators or calcimimetics. Parathyroidectomy (PTX) represents the ultimate treatment of hyperpara thyroidism in chronic dialysis patients after a medical treatment failure, particularly associating severe bone complications, and especially in a context where access to medical treatment remains limited **[5].** It has significantly reduced parathyroid hormone and is associated with long-term survival improvement **[6].** Persistent hypocalcaemia after surgical treatment of severe hyperparathyroidism is not uncommon **[7]** and may be secondary to transient or definitive hypoparathyroidism but also to bone-related pathology. Hungry bone syndrome (HBS) is a complication of hyperparathyroidism surgical management characterized by severe hypocalcaemia and hypophosphatemia secondary to a massive influx of calcium to an avid bone. We report the cases of two (2) patients operated for hyperparathyroidism secondary to chronic kidney disease (CKD).

Case Presentation 1

Mrs M. B. D is 43 years old, gravida 3 andpara 3, hypertensive known nine (9) years ago, currently treated under dual therapy (amlodipine 10 mg / day and perindopril 10 mg / day), peritoneal dialysis (DP) since 07/10/2016 for an CKD whose initial nephropathy is benign hypertensive nephropathy (HN). She is doing continuous ambulatory peritoneal dialysis (CAPD) four (4) daily exchanges. She has a history of orthopedic surgery for traumatic forearm fracture eight (8) years ago. A subtotal 7/8 PTX was performed on 11/09/2017 for the following indications: hyperparathyroidism with an elevated intact parathyroid hormone (iPTH) rated at 2452.4 pg / mL (N = 15-65 depending on the laboratory) or 37.7 times normal (37.7 N), bilateral parathyroid nodules measuring 7 mm and 8.3 mm on the right and 7.3 mm and 11.7 mm on the left. In addition, serum calcium was 92 mg / L, phosphoremia 41.4 mg / L, and 25 - OH vitamin D 20 ng / L. The laboratory investigations performed for immediate postoperative monitoring purpose outline dhypocalcaemia at 74.7 mg / L, hypokalaemia at 3.3 mmol / L. Then the patient had been put under calcium 500 mg and vitamin D 400 IU combined therapy with a dosage of one (1) tablet three (3) times daily. She was admitted on 14/09/2017 in nephrological hospitalization, on D4 postoperatively, on the basis of: neuromuscular signs featuring tetra paresis- associated muscular cramps and generalized tremor, a positive Chvosteksign, bone pain with predominant mechanical appearance at the pelvic level, uncontrollable immediate postprandial food vomiting associated with nausea, clinical anaemia. In emergency, we had severe hypocalcaemia at 55.8 mg / L (N = 84-104) corrected at 67 mg / L with albumin at 26 g / L (N = 35-50), mild to severe hypophosphatemiaat 19.4 mg / L (22 - 46), hypokalaemia at 2.8 mmol / L (N = 3.5 - 5.1), hyponatremia at 131 mmol / L (N = 136-145), and normochromic normocytic anaemia at 9.9 g / dL. The electrocardiogram recorded a regular sinus rhythm with no QT prolongation and no diffuse inverted T waves. The treatment had associated calcium gluconate 10 g in parenteral route and then relayed by bone calcium carbonate 9 g / day with 2 ug of un-alfa vitamin D, 2000 mg of potassium chloride and a free diet. In this post-PTX situation, the development of persistent severe hypocalcaemia with hypophosphatemia associating low calciuria at 46 mg / 24 h (N = 100 - 300) or 1.1 mmol / 24 h (N = 2.5 - 7.5), a iPTH that remains high at 1462.3 pg / mL (22.5N) and bone alkaline phosphatase (APL) elevated to 292.5 µg / l (N = 4.9 - 26.6) or 11N allows to raise the diagnosis of HBS in our patient (**Table 1**).

Table1. *Clinical characteristics of the patients.*

Data	Case 1	Case 2
Age (years)	43	44
Sex	Female	Female
Background	High blood pressure	High blood pressure
Dialysis method	Peritoneal dialysis	Haemodialysis
Dialysis duration (months) at time of PTX	11	49 of which 11 in PD
Initial nephropathy	HN	HN
Basic weight (kg)	48.3	52
Size (m)	1.65	1.68
BMI (kg / m^2)	17.7	18.4

PD: peritoneal dialysis. HN: hypertensive nephropathy.

Plasma Magnesium levels was normal at 18 mg / L. The change at twelve (12) months was outlined by triple hospital readmission for the same symptomatology with mean hypocalcaemia at 66.2 mg / l in a period of clinical stability, persistent hyperparathyroidism at 1924.2 pg / ml (30N) associated with vitamin D 25OH deficiency despite 100,000 IU of monthly Uvedose® with 2 g of un-alfa and 6 g of daily calcium supplementation (**Figure 1**).

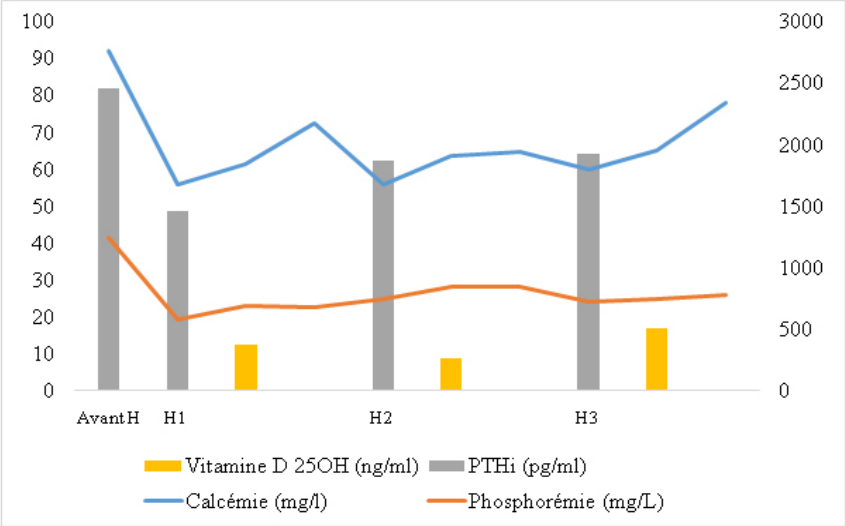

Fig1. *Evolution of serum calcium, phosphoremia and PTHi of case 1.H: hospitalization.*

Case Presentation 2

Mrs M.B, 44 years old, gravida 6 and para 5, hypertensive patient known five (5) years ago, now on dual therapy (amlodipine 10 mg / day and captopril 50 mg / day), under chronic haemodialysis since on 13/01/2013 after eleven (11) months of peritoneal dialysis. She does 3 weekly sessions of 4 hours with a dialy sate bath containing 1.5 mmol / L of calcium on a left radio radialarteriovenous fistula (AVF). She is anuric. A 7 / 8th subtotal PTX was performed on 07/03/2016 on the basis of secondary hyperparathyroidism with an intact parathyroid hormone (iPTH) raised to 2871 pg / mL (N = 15-65 depending on the laboratory) or 44N. Cervical ultrasound did not visualize the parathyroid glands. In pre-surgical period there was hypocalcaemia at 80.1 mg / L, a phosphoremia at 26 mg / L. On day 1 postoperative, the patient already described severe and diffuse bone pain, associating muscle cramps and persistent symptomatic hypocalcaemia 78.2 mg / L requiring a dialysis bath prescription containing 1.75 mmol / L of calcium with 4g of calcium gluconate during the session. In the inter-dialytic period she was administered 4.5 g of calcium with 1 µg of 1-alpha vitamin D. The lack of normal calcium levels restoration despite vitamin-calcium supplementation associating hypophosphatemia, a high iPTHlevels (19N) although having a decreasing curve lent support to make the diagnosis of an HBS (**Figure 2**).

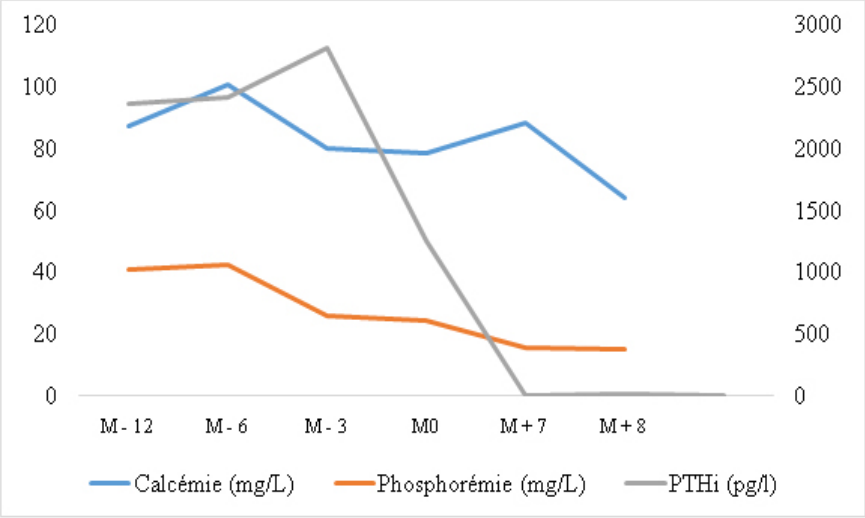

Fig2. *Evolution of serum calcium, phosphoremia and iPTH of case 2.M: months of operation.*

Seven (7) months after surgery, the patient developed bone fragility with multiple rib fractures. The diagnosis of adynamic osteopathy was made in the presence of definitive hypoparathyroidism at 6 µg/mL with hypocalcaemia at 75 mg/L, hypophosphatemia at 13.9 mg/L and 25-µ vitamin D deficiency at 25 ng/mL.

Discussion

The Diagnosis of HBS

HBS is defined by a decrease in a total serum calcium to2.1 mmol / L (84 mg / L) and/or prolonged hypocalcemia for >4 days after PTX, associated with hypophosphatemia and hypomagnesaemia **[8].** HBS may also be used when calcium supplementation is required to control postoperative calcemia despite optimization of supportive therapy (vitamin D, oral calcium, dialysis bath at 1.75 mmol / l of calcium) **[9].** This syndrome is most likely if bone turnover is very high **[7].** Bone avidity for calcium results from the abrupt decoupling between resorption and bone formation secondary to the loss of parathyroid hormone secretion after surgery. Calcium is mobilized from the blood compartment to the bone to repair severe demineralization. This results in hypocalcaemia despite major exogenous calcium intakes. Regarding our two (2) cases, the indication of PTX was raised by the indirect diagnosis of fibrous osteitis secondary to severe hyperparathyroidism with 37.7N and 44N iPTH. X-rays showed diffuse bone demineralization. They presented severe, symptomatic and sustainable hypocalcaemia after PTX. The persistence of elevated iPTH is induced by a secretion of the remaining parathyroid glands **[10],** and hypophosphatemia and low calciuria suggest involvement of another mechanism. In addition, none of the two (2) was given a bisphosphonate, which also decreased calciuria, phosphoremia, and phosphaturia (**Table 1**). HBS is thus secondary to the increased fall in iPTH after parathyroid exeresis, disrupting the bone turnover that was dependent on it, hence the increase in osteo formation (high alkaline phosphatases) compared to the resorption and mobilization of calcium and phosphorus from the bloodstream to the bone.

Patient Characteristics and Risk Factors of HBS

The incidence of HBS following PTX is variable in dialysis patients. According to the series, postoperative hypocalcaemia varies between 27.8 and 72% **[6].** We counted 18 patients operated for secondary hyperparathyroidism over a period of five years **[12],** i.e. a prevalence of HBS of 11.1% in Senegal. Several risk factors have been identified in the literature: the young age (47.5 years against 54.5 years), a high weight (60.7 kg against 49.8 kg), high ALP(415 IU / L against 221 IU / L) and preoperative hypocalcaemia (9.76 mg / dL vs. 10.4 mg / dL) and postoperative hypocalcaemia (7.1 mg / dL vs. 8.3 mg / dL) **[6, 13].** Our 2 patients were young with pre- and postoperative hypocalcaemia (**Table 2**).

Table2. *Evolution of the biological characteristics of the patients.*

Data		Case 1	Case 2
Preop	Calcium (mg / L)	92	80.1
	Phosphoremia (mg / L)	41.4	26
	iPTH (pg / mL)	2452.4	2871
	Vitamin D (ng / mL)	20	-
Postop day 4	Calcium (mg / L)	55.8	78.2
	Phosphoremia(mg / L)	19.4	16.6
	Magnesium (mg / L)	18	17.35
	iPTH (pg / mL)	1462.3	1246
	Bone APL (UI/L)	292.5	-
	Vitamin D (ng / mL)	12.6	-
Long-term	Calcium (mg / L)	66.2	75
	Phosphoremia (mg / L)	28.7	13.9
	iPTH (pg / mL)	1924.5	6
	Vitamin D (ng / mL)	17	25

Preop: preoperative. Postop: postoperative. APL: alkaline phosphatase. iPTH: intact parathyroid hormne.

Evolution at 12 Months

The treatment of this syndrome is based on a major supplementation of calcium and vitamin D. However it must be above all preventive and multidisciplinary involving nephrologist, surgeon and anesthetist-intensive care, based on the establishment of perioperative therapeutic protocols to minimize the risks of this syndrome. Case 1 was readmitted several times in hospital for severe attacks of symptomatic acute hypocalcaemia. Secondarily, she developed persistent hyperparathyroidism defined by high iPTH in the 6 months following PTX **[14].** The latter is noted at 3% in the literature **[15].** A cervicothoracic scintigraphy had not revealed ectopic parathyroid glands. Thus, this deep postoperative hypocalcaemia, strongly influenced by bone metabolism, requiring high doses of calcium and calcitriol occurring at high levels of iPTH (Table 3) is most likely related to HBS **[16, 17].** Case 2 has secondarily developed an a dynamic osteopathy complicating PTX but associated in our case with an excessive suppression of the secretion of iPTH during HBS treatment. In fact, this treatment requires the use of high doses of calcium (6 to 12 g / day) and calcitriol or alphacalcidiol (2-4 g / day) **[8].**

Conclusion

Hungry bone syndrome is a major complication of parathyroidectomy for hyperparathyroidism-associated high bone turnover. These two observations show out its management issues which must be extended but requires close monitoring in chronic dialysis patients.

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