HUNGRY BONE SYNDROME – REVISITED

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SUMMARY

Hungry bone syndrome is an important cause of prolonged severe hypocalcaemia following parathyroidectomy for hyperparathyroidism. More routine measurements of calcium, together with newer assays for parathyroid hormone, have increased the detection and treatment of milder hyperparathyroidism before the development of significant bone disease. Consequently, prolonged hypocalcaemia following parathyroidectomy – the hallmark of hungry bone syndrome – is rarely seen. It is still important to be aware of this potentially life-threatening complication, however. In most cases of hungry bone syndrome, hypocalcaemia is severe, symptomatic and requires prolonged treatment with intravenous calcium followed by vitamin D therapy for a considerable duration. This paper discusses the aetiopathogenesis, prevention and treatment of hungry bone syndrome.

INTRODUCTION

Transient, mild hypocalcaemia is common after parathyroidectomy (Table 1). After successful resection of a parathyroid adenoma for primary or tertiary hyperparathyroidism, serum intact parathyroid hormone (PTH) levels decline rapidly, often to undetectable concentrations, but usually returns to normal within 30 hours. Full PTH secretory response to hypocalcaemia may not return to normal for several weeks.[1, 2] Consequently, transient hypocalcaemia is frequently observed; in fact, mild hypocalcaemia reassures surgeons that the adenomatous gland has been successfully removed.[3] The commonest cause of hypocalcaemia following parathyroidectomy remains transient hypoparathyroidism due to suppression of the remaining parathyroid glands by preoperative hypercalcaemia. In hungry bone syndrome, there is a rapid influx of calcium into the bones, causing more prolonged hypocalcaemia. The incidence of hungry bone syndrome after parathyroidectomy can be as high as 12%.[2]

TABLE 1
Causes of hypocalcaemia after parathyroidectomy.

1. Temporary hypoparathyroidism
2. Permanent hypoparathyroidism
3. Hungry bone syndrome
4. Hypomagnesaemia
5. Acute calcitonin release following surgery

DIAGNOSIS

The diagnosis of hungry bone syndrome is based on significant symptomatic hypocalcaemia (often as low as 1·1 mmol/L), together with low or low normal serum phosphate and a rising serum alkaline phosphatase shortly after parathyroidectomy (Table 2). These are the markers of increased bone formation after the sudden withdrawal of PTH. Serum raised alkaline phosphatase is secondary to increased osteoblastic activity. Urinary calcium and phosphate concentrations are reduced, indicating total body deficiency.

TABLE 2
Diagnosis of hungry bone syndrome.

1. Persistently low serum calcium following parathyroidectomy
2. Low or low normal serum phosphate
3. Rising/raised serum alkaline phosphatase
4. Low urine calcium

AETIOPATHOGENESIS

The commonest aetiology of hungry bone syndrome is parathyroidectomy for hyperparathyroidism. The high serum calcium level in hyperparathyroidism is mainly due to increased bone turnover with increased osteoclastic bone resorption and increased renal tubular reabsorption of calcium. After parathyroidectomy the serum level of PTH falls dramatically as the unaffected glands have been suppressed by the hypercalcaemia. Consequently, the PTH-induced osteoclastic bone resorption stops, whilst the osteoblastic activity continues resulting in a marked increase in bone uptake of calcium, phosphate and magnesium.

With the increased detection of hyperparathyroidism in the asymptomatic stage, primary hyperparathyroidism is being treated before the development of parathyroid bone disease and the incidence of hungry bone syndrome is falling. Consequently, nowadays hungry bone syndrome associated with primary hyperparathyroidism is rarely seen, being more commonly associated with parathyroidectomy for tertiary hyperparathyroidism (i.e. from chronic renal failure). Again, improved recognition and treatment of secondary hyperparathyroidism has reduced the incidence of tertiary hyperparathyroidism. Such cases are now treated before the development of osteitis fibrosa cystica with a resultant drop in the incidence of hungry bone syndrome.

Hungry bone syndrome has also been reported after thyroidectomy for hyperthyroidism, usually in cases with a long duration of thyrotoxicosis prior to thyroidectomy (Table 3). Again, this is becoming less common as thyroidectomy is performed now after medical treatment has rendered the patient euthyroid, and also because with medical treatment thyroidectomy is done less commonly. The incidence can be as high as 50%.[5] Hungry bone syndrome has also been reported as a complication of renal tubular disorder with the correction of metabolic acidosis.[6] The mechanism responsible was thought to be remineralisation of the acidosis-induced demineralised bone with the correction of acidosis by alkali therapy.

TABLE 3
Aetiology of hungry bone syndrome.

1. After parathyroidectomy (commonest)
2. After thyroidectomy for hyperthyroidism
3. Correction of metabolic acidosis
4. Osteoblastic metastasis of prostate

Hypocalcaemia due to rapid accretion of calcium into bone has also been reported in several cases of metastatic prostatic carcinoma.[7-9] In two of these three cases hypocalcaemia was noted after oestrogen therapy. It is thought that osteoblastic activity of these metastatic tumours increases calcium uptake in the bone and this effect is further accentuated by oestrogen therapy, an antiresorptive agent. This theory is supported by the observation that other antiresorptive agents such as bisphosphonates, calcitonin and plicamycin, used to treat hypercalcaemia, may also result in hypocalcaemia.[10]

In untreated primary hyperparathyroidism serum magnesium concentration is usually low, appearing along with a deficit of total body magnesium. Parathyroid hormone stimulates renal tubular reabsorption of magnesium, but this is opposed by a direct tubular effect of hypercalcaemia.[11] Vomiting can enhance magnesium losses and/or pancreatitis associated with hypercalcaemia. Furthermore, after parathyroidectomy, renal wastage of magnesium is increased despite a low serum level of magnesium and total body deficiency.[12] Another reason for a further drop of serum magnesium concentration in hungry bone syndrome is increased bony uptake with remineralisation.

CLINICAL FEATURES

Severe, prolonged, symptomatic hypocalcaemia in the immediate post-operative period is the cornerstone of hungry bone syndrome. Acute hypocalcaemia is initially manifested by enhanced excitation of the peripheral nervous system; numbness, paraesthesia, muscular cramp, fasciculations and tetany. Chvostek's sign is elicited by tapping over the facial nerve approximately 20 mm anterior to the ear lobe below the zygomatic arch. Trousseau's sign represents carpal spasm secondary to ischaemia of the ulnar and median nerves in response to inflation of sphygmomanometer to 20 mm of Hg over systolic blood pressure. Severe hypocalcaemia may produce seizures, prolongation of the Q-T interval in the electrocardiogram and cardiac dysrhythmia.

Several risk factors have been described for the development of hungry bone syndrome after parathyroidectomy for hyperparathyroidism (Table 4). In a large series, hungry bone syndrome was noted in 25 of the 218 patients who underwent parathyroidectomy.[13] The higher the pre-operative serum calcium, alkaline phosphatase and PTH, the greater is the risk of developing post-operative hungry bone syndrome. The incidence increases as the size of the adenoma and age of the patient increases, although hungry bone syndrome has been well documented in children as young as six years of age.[14-16]

TABLE 4
Predictors of developing hungry bone syndrome.

1. Large parathyroid adenoma (>5 cm in diameters)
2. Higher pre-operative parathyroid hormone
3. Higher pre-operative serum calcium
4. Higher pre-operative serum alkaline phosphatase
5. Osteitis fibrosa cystica
6. Elderly (age >60 years)

TREATMENT

Careful monitoring of serum calcium in the immediate post-operative period (two to four times on the day of operation) is the key to the diagnosis. Treatment is started only when the symptomatic hypocalcaemia occurs, as hypocalcaemia is otherwise necessary to stimulate the remaining suppressed parathyroid glands to recover, and hypocalcaemia is the primary stimulator of these glands.

Treatment of severe hypocalcaemia is an endocrine emergency. Elemental calcium 100–300 mg (10–30 ml of 10% calcium gluconate) diluted in 150 ml of five per cent dextrose solution should be administered over ten minutes. If calcium gluconate is not available, calcium carbonate can be used, but this is quite irritating if extravasated.[17] Calcium can also be diluted in isotonic saline or water but should not be used undiluted, as concentrated solutions can cause thrombophlebitis. The intravenous calcium solution must not also contain bicarbonate or phosphate, which can form insoluble calcium salts. Such regimens do not increase serum calcium for more than two hours, and should therefore be followed by a continuous infusion of elemental calcium 0·5–1·5 mg/Kg/hour (1 mmol ten per cent calcium gluconate is equivalent to 10 mg of elemental calcium). Electrocardiographic monitoring during the infusion, whilst not mandatory, may be wise during rapid administration.

The intravenous calcium infusion should be continued until the patient is asymptomatic and tolerating oral calcium and vitamin 1,25 $(OH)_2D$ (calcitriol). Calcitriol is the preferred vitamin D preparation as the conversion of 25 to 1,25 $(OH)_2D$ requires 1α hydroxylation in the kidney, which is mediated by parathyroid hormone. In hungry bone syndrome, with the sudden withdrawal of parathyroid hormone, the activity of this enzyme is minimal. The duration of therapy is governed by the presence of symptoms and the severity of the hungry bone syndrome, and can be as prolonged as 29 months.[18, 19] Since bone mineral density has been noted to increase for one year after successful parathyroidectomy, it is prudent to continue calcium supplementation for one year.[20] Frequent measurements of urinary calcium are important to avoid progression of hypocalcaemia, to detect hypercalciuria and to guide adjustment of calcium and vitamin D therapy.

When significant hypomagnesaemia is associated with hypocalcaemia, it is best treated using the parenteral route. Up to 50 mmol/day can be administered safely in a patient with normal renal function. A large fraction of parenterally administered magnesium may be excreted in the urine, even in the presence of profound total body deficiency.[12] Many patients can excrete as much as 50–70% of the infused magnesium.[21] In hungry bone syndrome, hypomagnesaemia is usually corrected with the correction of hypocalcaemia.[12] In cases of hypophosphataemia, intravenous phosphate is avoided since phosphate can combine with calcium to produce a further drop in serum calcium concentration. An exception to this rule is the presence of severe hypophosphataemia (less than 0·31 mmol/L) where phosphate supplementation is necessary. The phosphate should be replaced by oral, intravenous or intraperitoneal routes in patients on dialysis.[22]

Severe hypocalcaemia and hungry bone syndrome can complicate parathyroidectomy in patients with end-stage renal disease. Treatment with prolonged and massive doses of calcium and calcitriol is often necessary. Calcium has also been given in the dialysate fluid.[18]

PREVENTION

The incidence of hungry bone syndrome following parathyroidectomy for primary hyperparathyroidism is decreasing because of:

1. early diagnosis of hyperparathyroidism;
2. treatment before the development of significant bone disease; and
3. improved pre-operative care with early recognition (Table 5).

Pre-operative treatment with calcitriol for a period of five to ten days with careful monitoring of the serum calcium may prevent the development of hungry bone syndrome. Tertiary hyperparathyroidism, due to chronic renal failure, is the main situation where this is now mostly seen. Whilst it is possible to predict who will develop hungry bone syndrome (Table 4), it is not guaranteed. In patients with chronic renal failure who are deemed to be at high risk of developing hungry bone syndrome, it has been suggested that intravenous calcitriol (2 mcg at the end of each haemodialysis treatment) be commenced three to five days prior to surgery and continued post-operatively to prevent hungry bone syndrome.[23]

TABLE 5
Prevention of hungry bone syndrome.

1. Awareness of the condition
2. Evaluation of the pre-operative predictors
3. Pre-operative treatment with vitamin D
4. Pre-operative treatment with bisphosphonate (possibly)

There is limited experience with bisphosphonates as a preventive measure for hungry bone syndrome.[24-26] Bisphosphonates, potent inhibitors of osteoclastic bone resorption, have long been used for the management of hypercalcaemia.[27] They have also been used as a medical treatment of hyperparathyroidism as a pre-operative measure to normalise the serum calcium, or in patients who are unsuitable for surgery.[28] Kumar and Ralston[25] reported a case of an elderly woman with primary hyperparathyroidism and significant bone disease who was treated with pamidronate infusion pre-operatively. In spite of the numerous risk factors for the development of hungry bone syndrome, it did not develop.[25] Graal and Wolffenbuttel[24] reported a young woman who developed severe hungry bone syndrome despite receiving pamidronate and vitamin D pre-operatively. Hamdy *et al.*[26] evaluated the role of pre-operative clodronate in cases of primary, secondary and tertiary hyperparathyroidism. The effect of clodronate in reducing the serum calcium was found to be ill sustained and suboptimal. They presumed that this pre-operative inhibition of osteoclastic bone resorption could be useful in the prevention of hungry bone syndrome in the post-operative period, although they did not look at the incidence of the same in their patients.

The exact mechanisms by which bisphosphonates exert these effects are not clear. It is probable that the potent inhibitory effects of bisphosphonates on osteoclast activity is the main mechanism. Furthermore, temporary cessation of mineralisation by bisphosphonates may help to prevent the development of the hungry bone syndrome.[29]

CONCLUSION

The possibility of developing hungry bone syndrome after successful removal of a parathyroid adenoma should be

borne in mind, particularly in cases where several pre-operative predictors are present. Pre-operative treatment with calcitriol is recommended, although the success rate needs further evaluation. When hungry bone syndrome develops, it should be treated aggressively with calcium and vitamin D. The role of bisphosphonates has yet to be established, but they may be helpful.

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