Primary Hyperparathyroidism-A Review of this Disorder and an Interesting Case Treated with Cinacalcet

Primer Hiperparatiroidizm-Hastalığın Gözden Geçirilmesi ve Cinacalcet ile Tedavi Edilen İlginç Bir Olgu Sunumu

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Abstract
Primary hyperparathyroidism is not an uncommon disorder and there can be a delay in the diagnosis as it remains mostly asymptomatic. We discuss about this disorder and review the literature. Treatment options which include both surgical and medical therapy are also discussed. We also report an interesting case of primary hyperparathyroidism which was treated with Cinacalcet. Turk Jem 2009; 13: 37-9

Key words: Primary hyperparathyroidism, surgery, cinacalcet, bisphosphonates, oestrogens

Özet

Anahtar kelimeler: Primer hiperparatiroidi, cerrahi, cinacalcet, bifosfanatlar, östrojen

Introduction
The parathyroid glands regulate serum calcium and phosphorus levels by secreting parathyroid hormone (PTH), which increases calcium level and lowers phosphorus concentration. Primary hyperparathyroidism (PHPT) is a disorder resulting in hypercalcaemia due to autonomous over-secretion of parathyroid hormone. We report an interesting case on this condition and discuss further about it, which would be of help both to a specialist and a general physician.

Case Report
A fifty-year-old lady presented with generalised body pains, constipation and polydypsia in February 1987. Her past history was not significant and there was no family history of note. Her corrected calcium was 3.61, phosphate 0.52, alkaline phosphatase 299 and PTH level of 152, consistent with a diagnosis of primary hyperparathyroidism. She had an isotope scan, which confirmed a left inferior parathyroid adenoma, which was removed two months later. Calcium remained around 2.5-2.9 for the next fifteen years and the patient was not on any medications though she still had generalised aches and pains associated with abdominal pain. Gastroscopy showed gastritis, and ultrasound of the abdomen revealed simple renal cysts. She was seen regularly in the endocrine clinic and calcium was monitored. She was admitted in March 2004 with pancreatitis, which was managed conservatively. Calcium was 2.69 but PTH was not checked. She was re-admitted again in November 2007 with pancreatitis, and calcium was 2.65 and PTH 284. Another admission was in December 2007 with acute pancreatitis, and calcium was 3.57 and PTH was 284. She had Sestamibi scan which raised a possibility of right inferior parathyroid adenoma surgically removed in February 2008. Post-operatively she still continued to have raised calcium. Hence she had CT scan of chest and abdomen, which showed unusual almost entirely
cystic right-sided retro-thyroid lesion, presumed to represent an unusual cystic parathyroid adenoma in the same region as noted on the previous scan. There was no evidence of mediastinal parathyroid adenoma. Endocrine surgeon was not likely to operate on her again, in view of possibility of her having adhesions due to previous two surgeries, making a repeat attempt difficult. Calcium remained between 2.7-2.9 post-operatively and PTH still remained consistently greater than 150. She was started on Cinacalcet 30 mg daily and calcium level gradually normalized. It has been within normal range for the last five months and she feels well.

Discussion

PHPT causes hypercalcaemia in view of excess production of PTH. This is usually due to a single parathyroid adenoma in about 97% of patients (1). Other rare causes include parathyroid hyperplasia, parathyroid carcinoma, adenomas in more than one gland, or an ectopic parathyroid adenoma. It can also be a feature of multiple endocrine neoplasia type 1 and type 2A, and familial hyperparathyroidism. It is a relatively common endocrine disorder and is the commonest cause for hypercalcaemia in the outpatient setting.

The classical symptoms that have been described are due to hypercalcaemia, and are summarised by the mnemonic ‘stones, groans, bones and moans’. ‘Stones’ refers to renal calculi, nephrocalcinosis and renal dysfunction. ‘Groans’ refers to gastrointestinal symptoms of constipation, abdominal pain, indigestion and vomiting, whilst ‘bones’ refers to complications of the bones in the form of osteitis fibrosa cystica, osteopenia, osteoporosis and pathological fractures. ‘Moans’ refers to neurological dysfunction in the form of fatigue, depression, memory impairment, psychosis and delirium. Untreated PHPT can be associated with cardiac manifestations such as congestive cardiac failure and left ventricular hypertrophy, and have impact on quality of life. However, most patients with PHPT are asymptomatic (2) and the diagnosis is usually made on routine laboratory finding of hypercalcaemia. Other biochemical abnormalities associated with PHPT include reduced serum phosphate level and elevated levels of blood urea nitrogen, creatinine, and alkaline phosphatase. The diagnosis is confirmed by the presence of hypercalcaemia associated with elevated or inappropriately normal PTH level. A 24-hour urine sample for calcium-creatinine ratio should be checked to distinguish PHPT from rare disorder of familial hypercalcaemic hypercalciiuria, where the ratio is below 0.01.

Parathyroid imaging has no role in the diagnosis of PHPT but is usually done to help the surgeon in identifying the anatomic localization of abnormally functioning or enlarged parathyroid glands (3). This may be done by ultrasonography, Sestamibi scan, CT scan or MRI scan, although all imaging studies can have false positive and false negative findings (3). Dual-energy x-ray absorptiometry (DEXA) scan is done to look at bone mineral density. Ultrasound or CT of abdomen is done to rule out renal calculi.

All patients with symptomatic PHPT should be referred for surgical treatment (3). Guidelines for parathyroid surgery in asymptomatic PHPT are summarised in the table below from the NIH workshop of 2008. If any of these criteria are met, the patient needs to be considered for surgery (4).

- Serum calcium >1.0 mg/dl (0.25 mmol/l) above normal
- Creatinine clearance below 60 ml/min /1.73 m²
- T score <-2.5 SD at spine, hip (total or femoral neck) or radius (distal 1/3 site) or presence of fragility fracture on DEXA scan
- Patients <50 years of age
- Patients in whom medical surveillance is neither desired nor possible.

Surgery still remains a matter of controversy in asymptomatic mild PHPT (5,6). Patients should be well hydrated and avoid medications which can cause hypercalcaemia, especially thiazide diuretics. Medical treatment options include: oestrogen, selective oestrogen receptor modulators (SERMs), bisphosphonates and Cinacalcet. The bisphosphonate, alendronate has been shown to increase lumbar spine and hip bone density in patients with PHPT, but serum calcium is unaltered (7). Oestrogen inhibits PTH-related bone resorption and stabilises bone density (8). Rubin et al showed a reduction in serum calcium and bone turnover markers by using raloxifene, a SERM in postmenopausal women with primary hyperparathyroidism (9).

Cinacalcet is a calcimimetic agent which increases the sensitivity of calcium-sensing receptors to extracellular calcium ions, thereby inhibiting the release of PTH. Shoback et al reported a randomized, double-blinded trial of 22 patients with PHPT receiving cinacalcet or placebo (10). The study demonstrated that mean serum PTH and calcium fell to the normal range with no consistent increases in urinary calcium excretion in the study subjects, indicating the potential benefit of cinacalcet as a treatment for primary hyperparathyroidism. Peacock et al randomly assigned 78 patients to cinacalcet or placebo to a one-year trial (11). It was found that cinacalcet normalized serum calcium in 73% of subjects compared with 5% of the placebo group. Serum PTH concentrations decreased by 7.5% with cinacalcet, but in the placebo group increased. However, further studies are needed to look at the long term effects of cinacalcet on bone mineral density.

Conclusion

PHPT is a relatively common disorder and recognition of this condition is crucial to prevent complications. The literature appears to indicate that calcimetics are an interesting new concept, and that Cinacalcet may be an effective, nonsurgical approach for management of PHPT.

Treatment of primary hyperparathyroidism

- Surgery
- Medical therapy
  - Bisphosphonates
  - Oestrogens
  - Selective oestrogen receptor modulators (SERMs)
  - Cinacalcet
- General Measures
  - Maintain adequate hydration
  - Avoid medications causing hypocalcaemia
  - Adequate calcium and Vitamin D intake
Key points
• Primary Hyperparathyroidism is a fairly common endocrine disorder and the diagnosis is usually made on routine laboratory testing.
• Most patients with the disorder are asymptomatic. All those who are symptomatic should be referred for surgery.
• There is data to suggest increase in mortality in untreated patients, especially related to cardiovascular disease.
• Recognition of this disorder is crucial, even from a general physician’s point of view to prevent complications.

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References