Primary hyperparathyroidism is a metabolic disorder in which there is hypersecretion of parathyroid hormone (PTH) from one or more hyperplastic or adenomatously affected parathyroid glands. There is usually an increase in size of parathyroid tissue, secondary to both an increase in the total mass of the tissue and an increased number of cells.

The most consistent abnormal finding in this disease entity is hypercalcemia. The overactive parathyroid glands are less sensitive to the suppressive effects of increased extracellular calcium and are relatively autonomous in their calcium regulation. The finding of a nonsuppressed PTH level by RIA in the presence of an increased serum calcium level confirms the diagnosis.

The etiology of primary hyperparathyroidism is not clearly defined. There is a history of irradiation to the neck in a reportable number of cases. The radiation dose reported has been variable, but the latent period may be upwards of thirty years. Primary hyperparathyroidism may also arise from the long term consequences of secondary hyperparathyroidism or long standing osteomalacia. Chronic loss of calcium through the kidney may also be a stimulus to an increase in size and activity of the glands and thus an uncontrolled secretion of hormone. Genetic predisposition to primary hyperparathyroidism has also been reported. Multiple endocrine neoplasia I syndrome (MEN I) is linked to genetic disarrangements of the q13 region of chromosome 11. Parathyroid lesions are found in over 80 percent of patients with MEN I (which also includes pancreatic and pituitary abnormalities). MEN II, which involves medullary carcinoma of the thyroid and pheochromocytoma has over 50 percent involvement with parathyroid disease as well.

Prevalence of hyperparathyroidism is somewhat more than previously realized. In one consecutive study of 26,000 calcium measurements, the incidence of primary hyperparathyroidism was about one in 1000. Not every one of these cases required treatment but was nonetheless present by diagnostic criteria.

Hypersecretion of PTH with primary hyperparathyroidism may be caused by a single adenoma of one of the four glands, primary chief cell or clear cell hyperplasia of all four of the glands, or carcinoma. The majority of cases appear to be caused by a single adenoma; in these instances one gland will enlarge while the others actually are suppressed and diminished in size. In hyperplasia, all four glands are involved. When MEN is the primary cause of parathyroid involvement, hyperplasia is almost always the rule. Parathyroid cancer probably accounts for between less than three percent of all cases. The malignant lesion is often palpable on physical exam and fixed to other local structures at the time of neck exploration. Local invasion, spread to regional lymph percent of cases and distant metastases are often described. The most marked levels of hypercalcemia are found with parathyroid carcinoma.

Until recently, primary hyperparathyroidism was considered a rare disease usually diagnosed in patients who presented with skeletal or renal manifestations. With mass automated chemical screening, the diagnosis has been picked up more commonly. Few cases have been reported in children or adolescents. In cases involving surgery, the sex ratio is approximately 3:1 favoring females with a peak incidence in the 51-60 age group (seven).

The degree of symptomatic hyperparathyroidism may vary from completely asymptomatic to profound signs of nausea, vomiting, weakness, fatigability, weight loss and depression. In its mildest form, there are no symptoms and the disease is only incidentally suspected from a routine measurement of serum calcium. A second form may develop slowly over months to years and often presents as renal colic. The most symptomatic of individuals progress quickly, with strikingly high blood calcium levels, debility, bone pain and pathological fractures. When renal symptoms prevail, renal colic is the most common symptom. Nephrocalcinosis and metabolic acidosis dominate the picture. Because PTH acts on the enzyme in the kidney that is responsible for the synthesis of 1,25 dihydroxyvitamin D, its concentration in plasma is elevated, causing hyperabsorption of calcium from the gut and an increased tendency to renal lithiasis.

Skeletal manifestations include osteitis fibrosa cystica, severe osteoporosis, bone cysts and so-called brown tumors (gum epulides or bony protuberances). Gout and pseudogout may be complications of the disease. Chondrocalcinosis and predisposition to attacks of pseudogout occur with relative frequency. Gout, with elevated levels of uric acid is also not uncommon and the increased uric acid excretion increases the risk of renal damage. Peptic ulcer occurs with increased frequency in primary hyperparathyroidism. Hyperparathyroidism as part of the MEN I syndrome may be the first manifestation of endocrine disease in the syndrome and in these families may precede the Zollinger-Ellison syndrome. Pancreatitis is another complication that is seen.
Neuromuscular manifestations (muscle weakness, thought to be secondary to nerve degeneration) and neurologic manifestations are also seen in primary hyperparathyroidism. Psychiatric symptoms may occur and range from mild depression to severe psychosis. Other associated abnormalities include polyuria and polydipsia, anemia, ectopic calcifications and a shortened Q-T interval on electrocardiogram in severe cases of hypercalcemia.

Laboratory studies show classic hypercalcemia and hypophosphatemia. Hypercalcemia is almost universally present reflecting the action of PTH on the kidney and the skeleton to increase resorption of calcium from the bone and the gut from stimulated 1, 25 dihydroxyvitamin D production. The significant serum calcium measurement is the concentration of ionized serum calcium. Nonionized serum calcium binds mainly to albumin, so sample results must be corrected for either abnormally low or high levels of albumin. In the absence of a specific measurement of ionized calcium, total calcium measurements should be adjusted 1:1 for either elevations or diminutions of albumin.

Generally normal laboratory ranges of serum calcium are between 8.5 and 10.5 mg/dl. Levels above 10.5 mg/dl after correction for serum albumin are suspicious for primary hyperparathyroidism. Suspicion increases when this is combined with a low serum phosphorus, a high urinary calcium excretion on a 24 hour sample, and a high level of parathyroid hormone (PTH). In normal circumstances a higher than normal level of calcium will shut off the secretion of PTH and render this level low or significantly suppressed; normal or higher than level normal PTH levels increase the likelihood of diagnosis of primary hyperparathyroidism.

When the diagnosis of primary hyperparathyroidism seems certain, localization of the problem becomes the next critical step. The four most diagnostic procedures commonly used are computerized tomography (CT), magnetic resonance imaging (MRI) and radioactive subtraction thallium-technecium imaging (TTS) and ultrasound. MRI is the most sensitive test with an accuracy of over 90 percent; all four are most accurate when an adenoma is present rather than hyperplasia of all four glands (7). When the diagnosis is still suspected but localization is in doubt, two invasive methods of preoperative localization- selective venous sampling of the internal jugular veins for PTH and arteriography of the thyroid vessels are available. These should be reserved for recurrent hyperparathyroidism or persistent hyperparathyroidism after initial cervical exploration.

No medical treatment is curative for primary hyperparathyroidism. Medical management is undertaken in certain circumstances. One is when patients refuse surgery for one reason or another. A second is when the risks of a surgical procedure make it too much of a risk because of other serious intervening problems. Another is when multiple surgical attempts have failed to cure the problem. A fourth circumstance is when affected individuals have normal calcium levels except during specific provocative instances (such as prolonged immobilization, vigorous diuretic therapy, etc.). Diuretics coupled with adequate hydration to increase urinary calcium excretion without dehydrating the patient is one method. Calcitonin, bisphosphonates, and certain chemotherapeutic agents (mithramycin) are also commonly used.

Surgical treatment of primary hyperparathyroidism remains the mainstay of successful outcome. Those with a primary adenoma most often return to a normal metabolic status after the adenoma is removed. Those with hyperplasia usually have three and one half glands removed of the four; the remaining active remnant usually is enough to maintain PTH secretion adequate for calcium balance without causing further stimulation of bone resorption and increased serum calcium.

In risk selection, two situations are addressed. First, coverage must be undertaken for the many possible side effects on various organ systems that untreated primary hyperparathyroidism can cause. Secondly, care must be undertaken to insure the adequacy not only of surgery to remove the cause of high serum calciums but also to insure that too vigorous exploration and excision might damage all glands enough to produce the opposite end of the spectrum (hypoparathyroidism, which has its own set of symptoms and long term sequelae).

When primary hyperparathyroidism is suspected and not treated, a low rating (+50/+75) is appropriate to cover complications such as renal, neurologic and skeletal abnormalities. When serum calcium (corrected, or by means of ionized calcium) is too high (over 11.5 mg/dl) for example, postponing definitive treatment is a wiser choice of action.

Those in whom surgical treatment has resulted in a long term favorable outcome can be offered standard insurance if there is no permanent end-organ involvement. A period of four to six months post surgery is probably advisable to insure that treatment is adequate enough to insure both that there will be no recurrent hyperparathyroidism and no hypoparathyroidism from injury to the remaining gland(s) post exploration. Postoperative hypoparathyroidism in surgery for hyperplasia is not uncommon due to transient bruising of the glands during exploration but this is usually transient and resolves within weeks following the procedure.

**Bibliography**