Evaluation and Management of Hyperparathyroidism

Embryology

In humans, the superior parathyroid glands are derived from the fourth branchial pouch, which also gives rise to the thyroid gland. The third branchial pouches give rise to the inferior parathyroid glands and the thymus. Location is important for surgical management. The superior parathyroid glands are most commonly found 80% at the upper and middle third of the thyroid lobe at the level of the cricothyroid junction (cricoid cartilage) and near the point where the recurrent laryngeal nerve passes beneath the inferior pharyngeal constrictor to enter the larynx. The inferior parathyroid glands are more varied in location and are usually found near the lower pole of the thyroid lobe below the lobe in the thyrothymic ligament. They also commonly lie below the inferior thyroid artery, anterior to the recurrent laryngeal nerve. Because of their more varied location than the superior parathyroids they may be more difficult to locate because of the longer migratory descent during development.

Hypercalcemia

Calcium is found in the bound form and the free ionized form. The bound form is not physiologically active. Forty-three percent of calcium is found in free ionized form in serum and this is physiologically active. The free ionized form reflects the regulation of PTH release and the balance between calcium influx into and calcium efflux out of the ECF. Hypercalcemia reportedly occurs in 1-4% of the general population and 0.2-3% of the hospital population. Excess PTH production or hyperparathyroidism is the most common cause of hypercalcemia. Hyperparathyroidism is the most common cause of hypercalcemia in non-hospitalized patients; malignancy is the most common etiology for hospitalized patients. The most common form of hyperparathyroidism is primary hyperparathyroidism.
Evaluation and Work-Up of Hypercalcemia:

Conventionally, hypercalcemia is associated with “moans, stones, groans, psychogenic overtones”. There can also be nonspecific symptoms, including fatigue, lethargy, and depression. Thirty to forty percent are asymptomatic. In the medical history, evaluate for meds that may lead to hypercalcemia including: lithium, thiazide diuretics, estrogen or androgens, and excess vitamin D. Physical exam includes vitals, examination of neck/lymphadenopathy, cardiovascular evaluation, respiratory and abdominal exams.

Lab measures include: PTH level/Calcium level, chemistry panel, 24hr urine calcium excretion, GFR and Vitamin D levels. Imaging centers around localization studies which include Sestamibi scanning and H&N US. CT or MRI can be used. KUB, IVP, or CT is considered for the evaluation of renal disease along with wrist, spine, and hip DEXA for evaluation of bone disease.

Types of Hyperparathyroidism

Primary Hyperparathyroidism (PHPT)

Parathyroid adenoma is the most common but other forms include parathyroid lipoadenoma, parathyroid hyperplasia, parathyroid carcinoma, and neck or mediastinal parathyroid cyst. It is estimated incidence is 1 case per 1000 men and 2-3 cases per 1000 women. The incidence increases above age 40. Most patients with sporadic primary hyperparathyroidism are postmenopausal women with an average age of 55 years. It is the most common cause of hypercalcemia; in fact, it is a rule that patients with hypercalcemia and elevated PTH have primary hyperparathyroidism until proven otherwise. As mentioned, the most common lesion found in patients with primary hyperparathyroidism is the solitary, benign parathyroid adenoma; greater than 80% of cases are caused by a solitary parathyroid adenoma and approximately 10% are caused by “double adenoma”. The diagnosis of primary hyperparathyroidism is confirmed by the biochemical findings of elevated calcium, elevated PTH, and elevated or normal levels of calcium in the urine. The serum calcium is not usually greater than 1mg/dl above the limits of normal. Low normal phosphate levels, elevated alkaline phosphate, high normal 1,25 OH2 Vit D, and normal GFR are seen with this presentation.

Secondary and Tertiary Hyperparathyroidism

Physiologic secondary hyperparathyroidism involves insufficient calcium intake, decreased intestinal calcium absorption, insufficient vitamin D intake or malabsorption; it represents the homeostatic attempt to maintain a normal serum calcium level by any means necessary. Pathologic secondary hyperparathyroidism and tertiary hyperparathyroidism occur as a result of renal insufficiency or renal failure. Subtle ionized hypocalcemia persisting over months to years leads to chronic stimulation of the parathyroid glands. Tertiary hyperparathyroidism is when the parathyroid glands may become autonomous after long-standing renal disease, and consequently no longer respond to regulation by serum ionized calcium. The clue is intractable hypercalcemia and inability to control osteomalacia despite
Vitamin D. Labs values reveal low normal Ca2+ and elevated PTH levels. GFR/CR are indicative of renal disease.

**Hypercalcemia of malignancy:**

Elevated calcium and PTH can result from paraneoplastic syndromes of malignancy. Examples include PTHrP release with lung, esophageal, H&N, renal, ovarian, and bladder cancer. Further, ectopic PTH is made by lung cancers and ovarian cancers. Ectopic 1,25 OH Vitamin D is made by various lymphomas including B cell lymphoma and Hodgkin's lymphoma.

**MEN 1 and 2a (Sipple Syndrome):**

Inheritance is autosomal dominant. PHPT is often the first and most common endocrinopathy of MEN 1 and reaches nearly one-hundred percent penetrance by age 50. Pituitary, pancreas, and parathyroid disease is seen in MEN 1. Pancreatic islet cell tumors occur in 60 to 70% of patients. Prolactinoma is the most common pituitary tumor. Recognition of PHPT in a YOUNG adult (usually by the 2nd decade) can lead to the discovery of MEN 1. The presence of a tumor involving of the three organ systems in a first degree family member also confirms the presence of familial MEN 1. Angiofibroma are commonly associated with MEN 1 and are reported in 5%, 8%, 22%, 43%, 64%, and 88% of patients with MEN1. Lipomas and collagenomas are also associated.

Men 2a or Sipple’s syndrome is also autosomal dominant. It is associated with MTC (100%), pheochromocytoma, and parathyroid disease(70%) and involves a dermaline mutation of the RET-proto-oncogene located on chromosome 10. Screening for medullary thyroid carcinoma is done with the pentagastrin stimulation test, measuring serum calcitonin at baseline and at 2, 5, and 10 minutes. Upon a diagnosis of MTC, a urinary catecholamines and metanephrines screen is done for pheochromocytomas and gene testing for family members is performed.

**Familial Hypercalcemic Hypocalcuria (FHH)**

Autosomal dominant and typically presents during childhood. The serum calcium is mildly to moderately elevated BUT urine calcium is normal to low normal (which is abnormal in the setting of elevated blood calcium). A 24 hour urine calcium and creatinine clearance yielding a ratio of <0.01 is seen and there is a positive family history. Generally, these patients are asymptomatic and no treatment is required. The pathophysiology is due to a mutation of the calcium-sensing receptors of parathyroid cells (CASR gene)

**Operative Management**

**Pre –op localization studies**

Sestamibi scan is most commonly used closely followed by head and neck ultrasound. The sensitivity for various modalities are as follows:
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- Tc 99M sestamibi: 70-91% sensitive (88%)
- Ultrasound: 35-75% sensitive (88.5%)
- CT: 42-68% sensitive
- MRI: 57-88% sensitive
- Selective venous cath: up to 80% sensitive

Tc 99m sestamibi scan was first proposed in 1992 by Taillefor et al. The patient is injected with 20-25mCi of Tc 99m sestamibi. Subsequent images are taken at 10-15 minutes and again at 2-3 hours since thyroid and thyroid nodules clear uptake faster than parathyroid neoplasms do. Tc 99m is incorporated into the cytoplasm and mitochondria. Parathyroid tissue has a large number of mitochondria in its oxyphil cells compared to thyroid tissue, thus allowing Tc99m to enter parathyroid tissue more intensely. Limitations to this study is a 1% to 3% false-positive rate and it cannot identify multiglandular disease.

Parathyroid surgery

A clear indication for surgery is most obviously a clearly symptomatic patient. The controversy arises with the asymptomatic patient to be discussed below. Bilateral parathyroid exploration is the gold standard but is being phased out. Unilateral parathyroid exploration, when performing parathyroidectomy for primary hyperparathyroidism, is exploration on the side there is a definite adenoma. The ipsilateral normal gland is examined but the contralateral glands are not examined. Rationale for this approach is that greater than 85% of cases of sporadic hyperparathyroidism are caused by a solitary adenoma. These groups hypothesized that the morbidity associated with a standard four-gland parathyroid exploration could be minimized with a less invasive procedure while maintaining the same level of success at curing the disease. Subsequent reports based on similar principles have concluded that unilateral exploration can be performed with results comparable to a bilateral exploration. Limitations of this technique is unilateral parathyroid exploration is limited by the intrinsic 15% rate of multiglandular primary hyperparathyroidism, combined with the imperfections of preoperative localizing techniques.

Special consideration: The Asymptomatic patient

Three International Workshops by the NIH to date that have proposed and refined the indications for parathyroidectomy in asymptomatic patients. Why is this important? Most patients with primary hyperparathyroidism are asymptomatic. A recommendation for invasive surgery is not always readily accepted by these patients. In the third workshop, the following recommendations were made. Asymptomatic patients meet criteria for surgery if:

- Is greater than 1mg/dL above the upper limit of normal
- If creatinine clearance is reduced to <60ml/min
- If the BMD T score is <-2.5 at any site and/or previous fracture fragility
- If the patient is less than age 50
• In patients for whom medical surveillance is neither desired nor possible

For patients who do not meet criteria, serum calcium and creatinine should be monitored annually. Bone mineral density should be measured every 1-2 years at three sites.

Minimally Invasive Surgery

Though the concept of unilateral exploration was introduced as early as 1981, parathyroidectomy with less than four-gland exploration did not gain wide acceptance until the 1990s, when a number of different minimally invasive techniques were introduced. Initially, movement was market/patient driven and not evidence based. Various definitions of minimally invasive surgery have arisen since. Brunaud et al defined minimally invasive surgery as “used only to describe thyroid and parathyroid procedures that are routinely associated with an incision shorter than 3.0 cm for thyroidectomy and 2.5 cm for parathyroidectomy”. Other forms of minimally invasive surgery include:

• Videoendoscopic – gasless technique
• “Video-assisted” (MIVAP)
• Radioguided (MIRP)
• Focused central mini-incision (2.5 cm, direct view)
• Focused lateral mini-incision (1.5-2.0 cm, direct view)

The focused mini incision minimally invasive parathyroidectomy involves scan-directed removal of a single adenoma through a 2.0-cm mini-incision without intraoperative monitoring. This technique was reviewed by Pang et al in a study group comprised 500 consecutive patients undergoing MIP via a lateral mini-incision from August 2000 to September 2005. Levels of parathyroid hormone (PTH) were measured after operation solely to aid informed discharge. They found that using this technique had a cure rate of 97.4 per cent was achieved in 500 consecutive patients. These results were equivalent to those in most other published series of both open parathyroidectomy and minimally invasive techniques using a variety of open, endoscopic or video-assisted techniques, and employing either intraoperative PTH measurement, a nuclear probe, or both. They also found that the lateral incision has better access to parathyroid-bearing tissue then central mini incision and this technique was less complex than the video-assisted techniques.

The minimally invasive video-assisted parathyroidectomy (MIVAP) has been most evaluated by Miccoli. In a study by his group in 2004, they review the technique. The MIVAP procedure is characterized by a single central (or lateral) access of 1.5 to 2 cm at the notch level. The technique relies on external retraction, thus no insufflation is performed in the neck. The midline is carefully individuated and incised, and the strap muscles are separated from the thyroid lobe by gentle blunt dissection, performed under direct vision, on the side of the suspected adenoma. The endoscopic instruments are then introduced. In their case, they used a 30 degree 5 mm endoscope for magnification, other 2 mm instruments such as spatulas and
forceps, and 2 mm titanium clips. The found that surgery was successful 94% of the time and the mean operating time was 36 minutes. Neither persistent nor recurrent disease has increased significantly and this technique did not expose patients to a high complication rate. The two most common complications in patients undergoing surgery for PHPT are recurrent nerve palsy and hypoparathyroidism. Complication rates were less than 1% (0.8%) in this study.

Compared to MIVAP, the videoendoscopic –insufflation or gasless uses CO insufflation. The “gasless” technique involves a 3-minute CO2 insufflation (12 mm Hg) through a conventional trocar inserted under the strap muscles is used just to anatomically dissect the virtual thyrotracheal groove. Actually, the working space is maintained by means of skin retractors so as to allow needlescopic instruments to perform a parathyrodeectomy with the gasless procedure. The “insufflation” procedure uses CO2 insufflation for the duration of the case. The use of CO2 insufflation is being phased out, especially with the “insufflation” technique as there is an increased risk of the hemodynamic variables being affected (tachycardia and decreased MAP) and subcutaneous emphysema.

Minimally invasive radioguided parathyroidectomy (MIRP) was first described by James Norman in the 1990’s. This technique involves the use of “intraoperative nuclear mapping in-patients identified by Sestamibi scanning to have a single adenoma in hopes of minimizing operative intervention while maintaining the efficacy of a full exploration”. Specifically, patients underwent Sestamibi scanning within 3 hours of surgery. A gamma probe is then used to measure radioactivity in four quadrants of the neck, defined by the upper and lower poles of the thyroid gland on each side. The area of radioactivity guides incision placement and intraoperative dissection (intraoperative mapping) to the adenoma. Further, once the adenoma has been identified and removed, the gamma probe measures the radioactivity of the adenoma removed while on the specimen table to ensure it was appropriately removed. They were able to find the adenoma in an average of 19 minutes and intraoperative nuclear mapping complemented Sestamibi scanning to help distinguish single-gland from multigland disease. Further, this technique allows for a minimally invasive operation under local anesthesia in a true outpatient setting. Of note, in a discussion addendum to this study, it was noted that not all institutions are equipped for expeditious Sestamibi scanning and quick transport to the OR (within 3 hours of the study). In such a case, this technique is not recommended.

Complications of surgery:

As compared to traditional surgery, minimally invasive surgery shares the same complications which includes persistent disease, recurrent disease, hypocalcemia, and RLN injury. There are no increased complications rates when comparing minimally invasive surgery to traditional surgery (unilateral parathyroid exploration).
Sources

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