Parathyroid Surgery

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AAO-HNSF/AHNS SISSON SYMPOSIUM
Review Course for Residents & Fellows
September 28th 2013

History

- In 1852, Sir Richard Owen first described the parathyroid glands during a post-mortem examination of an infant rhinoceros.
- In 1879, Sandström, a Swedish surgeon, described the parathyroid glands in humans.
- In 1891, von Recklinghausen described osteitis fibrosa cystica, which was later associated with parathyroid hormone (PTH).
- Calcium measurement became possible in 1909, and its association with PTH was established.
- In 1925, Mandl performed the first parathyroidectomy in a 38-year-old man with severe bone pain due to osteitis fibrosa cystica. The patient was initially symptom-free but developed recurrent bone problems 6 years later.
- In 1926, the first parathyroidectomy in the United States was performed at Massachusetts General Hospital by a 5-year-old girl with osteitis fibrosa cystica.
- In 1934, Albright reported on the association between parathyroid disease and chronic renal failure.
- 1977 Nobel prize for sequencing of parathyroid hormone.

Anatomy

- Usually derive most of blood supply from branches of inferior thyroid artery, although branches from superior thyroid supply at least 20% of upper glands.
- Glands drain ipsilaterally by superior, middle, and inferior thyroid veins.
• The superior parathyroid glands are most commonly located in the posterolateral aspect of the superior pole of the thyroid gland at the cricothyroidal cartilage junction.
• They are most commonly found 1 cm above the intersection of the inferior thyroid artery and the recurrent laryngeal nerve.
• The inferior parathyroid glands are more variable in location and are most commonly found near the lower thyroid pole of the thyroid.

Parathyroid Embryology
• The PTH glands develop at 6 weeks and migrate caudally at 8 weeks.
• The superior PTH glands develop with the thyroid gland from the fourth branchial pouch and are generally consistent in position, residing lateral and posterior to the upper pole of the thyroid at the level of the cricothyroid cartilage.
• The inferior PTH glands descend with the thymus from the third branchial pouch.

Histology
• The four PTH glands are composed mostly of chief cells and oxyphil cells within an adipose stroma.
• Chief cells in the PTH glands secrete PTH, an 84–amino acid protein, whenever serum calcium levels fall.
• Almost all of the PTH is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain.
• PTH binds to its peripheral receptors and stimulates osteoclasts to increase bone resorption, to the kidney, to increase calcium resorption and renal production of 1,25-[OH]$_2$D$_3$, and to the intestine to increase absorption of calcium and phosphate.
• All together, these processes raise the serum calcium level.

Calcium physiology
• PTH-calcium feedback loop that controls calcium homeostasis.
• Four organs—the parathyroid glands, intestine, kidney, and bone—together determine the parameters of calcium homeostasis.
• PTH secretion also is stimulated by low levels of 1,25-dihydroxy vitamin D, catecholamines, and hypomagnesemia.
Primary Hyperparathyroidism

- Affects approximately 100,000 patients a year
- Primary hyperparathyroidism occurs in 0.1 to 0.3% of the general population and is more common in women (1:500) than in men (1:2,000)
- Primary hyperparathyroidism is characterized by increased parathyroid cell proliferation and PTH secretion which is independent of calcium levels
- The most common cause of primary hyperparathyroidism is a sporadic, single parathyroid adenoma resulting from a clonal mutation (~85-95%)
- Less common are parathyroid hyperplasia (~2.5%), parathyroid carcinoma (malignant tumor), and adenomas in more than one gland (together ~6.5%).
- Primary hyperparathyroidism is also a feature of several familial endocrine disorders: MEN type 1 and MEN type 2A, and familial hyperparathyroidism.

Secondary Hyperparathyroidism

- When HPT is seen in the setting of chronic renal failure, it is termed secondary HPT
- 90% of patients with chronic renal failure have some evidence of secondary HPT
- Failing kidneys do not convert enough vitamin D to its active form, and they do not adequately secrete phosphate. When this happens, insoluble calcium phosphate forms in the body and removes calcium from the circulation
- Secondary hyperparathyroidism can also result from malabsorption (chronic pancreatitis, small bowel disease, malabsorption-dependent bariatric surgery) in that the fat soluble vitamin D cannot be reabsorbed.
- With prolonged stimulation of the parathyroids, a disorder termed tertiary HPT chronic renal failure or those with long-standing secondary HPT who undergo kidney transplantation. Autonomous hyperfunction develops and the parathyroids no longer respond to calcium feedback inhibition, which results in hypercalcemia.

Diagnosis and clinical features

- Before advent of the serum channel autoanalyzer, patients with primary HPT were typically seen with the clinical manifestations of hypercalcemia
- Hypertension - one third of patients with HPT
- Nonspecific complaints such as fatigue, lethargy, and depression are most commonly cited
- Less than 5% have evidence of osteitis fibrosa cystica
- Less than 20% of primary HPT patients have renal symptoms
- Before advent of the serum channel autoanalyzer, patients with primary HPT were typically seen with the clinical manifestations of hypercalcemia
- The diagnosis is made by demonstrating elevated serum calcium and intact PTH (iPTH) levels and normal or increased urinary calcium levels in the setting of normal renal function
- A 24-hour urine collection can help exclude the diagnosis of benign familial hypercalcemia (BFHH)
- Middle-aged and older women are most commonly affected by the disease
- It is characterized by hypersecretion of PTH, leading to hypercalcemia
- With prolonged stimulation of the parathyroids, a disorder termed tertiary HPT chronic renal failure or those with long-standing secondary HPT who undergo kidney transplantation. Autonomous hyperfunction develops and the parathyroids no longer respond to calcium feedback inhibition, which results in hypercalcemia.

Diagnosis and clinical features

- Serum values of the serum calcium autoanalyzer, patients with primary HPT were typically seen with the clinical manifestations of hypercalcemia
- Trichina
- Parathyroid, kidney stones, abdominal groans, “psychic pains,” and fatigue complaints
- Under the age of 10, 10% of patients present with nephrocalcinosis

NOW

- Less than 30% of primary HPT patients have renal symptoms
- Less than 5% have evidence of systemic fibrosis
- Nonspecific complaints such as fatigue, lethargy, and depression are most commonly cited
- Hypertension one third of patients with HPT
Labs

- Confirm Hypercalcemia present
- Eliminate potential causative medications
- Obtain intact Parathyroid Hormone (PTH) Level
- PTH normal or high: Obtain 24 hour Urine Calcium
  - 24 hour Urine Calcium normal or high
    - Primary Hyperparathyroidism
    - Recovery from Acute Tubular Necrosis
    - Lithium therapy
  - 24 hour Urine Calcium low
    - Familial benign hypocalcemic hypercalcemia

Indications for Surgery in Asymptomatic Patient w/ Primary HPT - NIH Consensus(1990)

- Serum calcium concentration >1 mg/dL (>0.25 mM/liter) above the upper limits of normal (markedly elevated serum Ca++) or episode of life-threatening hyperCa++
- Reduced creatinine clearance; renal stones
- Bone density at the lumbar spine, hip, or distal end of the radius that is >2 SD below peak bone mass (T-score <−2.5)
- Individuals with primary hyperparathyroidism <50 yr
- Patients for whom medical surveillance is undesirable or impossible

Preoperative localization in Patients With Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
<th>COST</th>
<th>SAFETY</th>
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<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
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<tr>
<td>Sestamibi</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Safe</td>
<td></td>
</tr>
<tr>
<td>Sestamibi SPECT</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Safe</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Safe</td>
</tr>
<tr>
<td>4D-CT</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Radiation</td>
</tr>
<tr>
<td>MRI</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Safe</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Radiation</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Angiography</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Very high</td>
<td>Hematoma, CVA, nephropathy*</td>
</tr>
<tr>
<td>Venous localization</td>
<td>High</td>
<td>High</td>
<td>Very high</td>
<td>Hematoma, infection</td>
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</tr>
<tr>
<td>4D-CT, Four-dimensional CT</td>
<td>High</td>
<td>High</td>
<td>Very high</td>
<td>Hematoma, CVA, nephropathy*</td>
</tr>
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Substraction

- Thallium (Tl) scan 1st
  - Thyroid and parathyroid
  - Allow for washout from both
- Follow with Technetium (Tc) scan
  - Thyroid only
- Tc image (thyroid) is subtracted from Tl image (thy + parathy) to get parathyroid image itself
Ultrasound

- Ultrasound is effective, noninvasive, and inexpensive, but its limitations include operator dependency and restriction to application in the neck because it cannot image mediastinal parathyroid lesions.
- It has a 48% to 74% true-positive rate.
- Ultrasound often is used in combination with sestamibi, in which case the combined true-positive rate rises to 90%.

Sestamibi washout scan

- 99mTc 2-methyl-isobutyl-isonitrile radionuclide (Tc-sestamibi)
- Discovered in 1989 to be useful in imaging of parathyroid glands.
- Radioisotope uptake increases with gland weight.
- MIBI concentrated in tissues rich in mitochondria:
  - Heart
  - Salivary glands
  - Thyroid glands
  - Parathyroid glands

SPECT

- Increases the accuracy of routine Sestamibi scanning by about 2 to 3 percent.
- We had been using SPECT imaging for all patients in which there is a questionable adenoma (about one in 20-30).
- SPECT scanning can be performed at any time within the first several hours after a patient is injected with the radioactive Sestamibi radiopharmaceutical.
- During the scan, 30 (typical) or more images are taken surrounding the patient’s head and neck.
- When ordinary Sestamibi scans are inconclusive or reoperation is necessary, SPECT/CT fusion is performed. SPECT/CT fusion refers to the imaging technique that combines the functional information from SPECT with the anatomical information from CT into one set of images.
Cross sectional imaging - CT, MRI, 4D-CT scan

- Cross-sectional imaging useful for visualizing mediastinal tumors and glands within the tracheoesophageal groove.
- MRI - parathyroid adenomas often appear intense on T2-weighted images.
- CT is less expensive and has a sensitivity of 70% and a specificity of nearly 100%.
- Four-dimensional CT (4D-CT), a novel imaging modality similar to CT angiography, is derived from three-dimensional (3D)-CT scanning with an added dimension from the changes in perfusion of contrast over time.
- In a study of 75 patients with primary HPT, a novel CT is less expensive and has a sensitivity of 70% and a specificity of nearly 100%.

Invasive Preoperative Localization

- A subset of patients who require localization will have negative, discordant, or non-malignant adenoma localization studies.
- These patients may undergo invasive localization in the angiography suite, where rapid PTH measurement is now being performed.
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Surgery for primary hyperparathyroidism

- Bilateral Neck Exploration
- Minimally Invasive Parathyroidectomy

Bilateral Neck Exploration

- The classic approach to the surgical management of primary HPT traditionally has been bilateral neck exploration under general anesthesia, with intraoperative, histopathologic frozen section examination of excised parathyroid tissue.
- Ideally, all the parathyroid glands are identified, and the surgeon removes the pathologically enlarged gland or glands.
- Historically, patients were admitted to the hospital for 1 or 2 days and failure rates in the best series were consistently less than 3% to 5%.
- Standard bilateral neck exploration is still considered an excellent operation, with a complication rate in the 1% to 2% range and a cure rate (defined as normocalcemia 6 months postoperatively) higher than 95%.
Minimally Invasive Parathyroidectomy (a.k.a. MIP, guided, focused, directed)

- Because 85-95% of primary HPT results from a single adenoma and is cured by excision of the offending gland-directed surgery after accurate preoperative localization has been used with increased frequency.
- MIP involves the use of unilateral neck surgery under regional or local anesthesia in the ambulatory setting.

Handheld gamma detection device employing a parathyroid probe

Surgery Steps
• 305 patients who underwent MIRP in our institution between 1997 and 2007
• Data including symptoms, pre and post-operative calcium levels, and PTH levels were collected
• Evaluate the efficacy of Minimally Invasive Radioguided Parathyroidectomy (MIRP) based on:
  – Pathology
  – Calcium levels
  – Parathyroid hormone levels
  – Symptoms & signs

Results
• 100% Intraoperative frozen pathology specimens were hypercellular parathyroids
• 100% Permanent pathology specimens were parathyroid adenomas

<table>
<thead>
<tr>
<th></th>
<th>Pre-Op</th>
<th>Post-Op</th>
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</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>10.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Ionized Ca</td>
<td>1.45</td>
<td>1.23</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>138</td>
<td>50</td>
</tr>
<tr>
<td>Rapid PTH</td>
<td>270</td>
<td>50</td>
</tr>
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Secondary hyperparathyroidism
• Typically managed initially medically, (vitamin D analogues & calcimimetic agents (e.g., cinacalcet)

Indications for surgery: severe refractory complications:
• Renal osteodystrophy (osteitis fibrosa cystica, osteomalacia, and adynamic bone disease)
• Uremic pruritus, or severe itching with end-stage renal failure,
• General weakness is common in uremic patients,
• Anemia is common in uremic patients
• Calciphylaxis is a rare, severe, and life threatening complication of secondary HPT characterized by calcification of the media of small to medium sized arteries; it results in ischemic damage in dermal and epidermal structures. Calcification can lead to nonhealing ulcers, gangrene, sepsis, and death

Surgery Other
• Video assisted
• Endoscopic
• Robotic
• Reoperative
Surgical Strategies

- Generally, preoperative imaging before initial parathyroidectomy for secondary HPT is not indicated because bilateral neck exploration is required for identification of all glands, given that the underlying pathology is parathyroid hyperplasia
- Subtotal parathyroidectomy
- Total parathyroidectomy with heterotopic autotransplantation

Secondary Hyperparathyroidism

- Surgical treatment is indicated and recommended for patients with
  - bone pain,
  - pruritus, and a calcium-phosphate product >=70,
  - Ca greater than 11 mg/dL with markedly elevated PTH
  - Calciphylaxis
  - progressive renal osteodystrophy,
  - soft-tissue calcification

Tertiary Hyperparathyroidism

- Long standing renal failure s/p renal transplant
- autonomous parathyroid gland function and tertiary HPT.
- Can cause problems similar to primary hyperparathyroidism
- Operative intervention
  - symptomatic disease
  - autonomous PTH secretion persists for more than 1 year after a successful transplant
- subtotal or total parathyroidectomy with autotransplantation
**Multiple Endocrine Neoplasia**

- **MEN1 syndrome**: Primary HPT resulting from parathyroid hyperplasia associated with lesions of the pancreas and pituitary.
- The parathyroid glands are asymmetrically enlarged and there is a high incidence of supernumerary glands (up to 20%).
- Parathyroid surgery in patients with MEN1 is thought of as a debulking or palliative procedure because recurrence is inevitable if survival is unlimited; it is indicated to treat and prevent the complications of HPT.
- The initial surgical procedure of choice in a patient with MEN1 and HPT is subtotal parathyroidectomy or total parathyroidectomy with heterotopic autotransplantation of resected parathyroid tissue; transcervical thymectomy is also performed at the initial operation.
- (Cryopreservation of parathyroid tissue is performed at the time of total parathyroidectomy whenever possible).

- **MEN2A syndrome**:
  - is marked by the findings of medullary thyroid cancer, pheochromocytoma, and primary HPT.
  - HPT in MEN2A is the least common manifestation and occurs in 20% to 30% of patients.
  - HPT in MEN2A differs from MEN1 in several important features, and the indications for parathyroidectomy and diagnostic criteria are more similar to those of sporadic primary HPT.
  - When compared with HPT in MEN1, HPT in MEN2A tends to be milder and more often asymptomatic because of a single adenoma, although multiglandular hyperplasia does occur. Therefore, curative resection can be less aggressive.
  - Enlarged parathyroids encountered during thyroidectomy for medullary thyroid cancer in a normocalcemic patient are resected.
  - Most but not all endocrine surgeons leave normal-appearing parathyroids in situ, although total parathyroidectomy with autotransplantation to the forearm has been advocated by some.

**Parathyroid Carcinoma**

- Parathyroid carcinoma is the least common endocrine malignancy, accounting for 0.005% of all cancer cases in the US.
- Most patients with carcinomas have marked hypercalcemia (>14 mg/dL) and are more likely to have associated bone and renal disease than those with adenomas.
- Extremely high iPTH level, a palpable neck mass on physical examination, significant uptake on sestamibi scan, or ultrasound evidence of invasion with loss of planes between the parathyroid and thyroid, occasionally with lymphadenopathy.
- Initial aggressive surgical approach involving en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of adjacent soft tissues is performed because this is the only potentially curative treatment.
- En bloc resection is associated with a 40% local recurrence rate and an overall survival rate of 89% (mean follow-up, 119 months).
- Distant metastases generally develop in the lungs, liver, and bone; they can occasionally be treated by resection of individual tumor deposits. Generally, control of hypercalcemia by surgical resection of metastases or local recurrence is more effective than medical treatment.
- Most patients with metastatic or locally unresectable disease die of the metabolic effects of uncontrolled hypercalcemia.
- There are still no generally accepted staging systems for parathyroid carcinoma.

### Table 5.1 Parameters associated with HPT and multiglandular disease

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genetic defect</th>
<th>Incidence of HPT</th>
<th>Clinical/Pathologic Features</th>
<th>Therapy of HPT</th>
</tr>
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<tbody>
<tr>
<td>MEN1</td>
<td>MEN1 (mond)</td>
<td>10–100%</td>
<td>Parathyroid hyperplasia, adenoma, primary HPT, FOP, osteoporosis</td>
<td>Initial aggressive surgical approach involving en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of adjacent soft tissues is performed.</td>
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<td>MEN2A</td>
<td>RET</td>
<td>&gt;10%</td>
<td>Parathyroid hyperplasia, primary HPT, FOP, osteoporosis</td>
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</tr>
<tr>
<td>Familial</td>
<td>JEA, FOP, HPTA</td>
<td>100%</td>
<td>Parathyroid hyperplasia, adenoma, primary HPT, FOP, osteoporosis</td>
<td>Initial aggressive surgical approach involving en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of adjacent soft tissues is performed.</td>
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<tr>
<td>HPTA</td>
<td>FOP, HPTA</td>
<td>10–100%</td>
<td>Parathyroid hyperplasia, adenoma, primary HPT, FOP, osteoporosis</td>
<td>Initial aggressive surgical approach involving en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of adjacent soft tissues is performed.</td>
</tr>
<tr>
<td>HPTA-IT</td>
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<td>80%</td>
<td>Parathyroid hyperplasia, adenoma, primary HPT, FOP, osteoporosis</td>
<td>Initial aggressive surgical approach involving en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of adjacent soft tissues is performed.</td>
</tr>
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<td>FOP</td>
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*For a comprehensive review, refer to Marx and Solcia (2009) [10]*
Secondary (revision) parathyroid survey:

- Examination for abnormal parathyroids in locations beyond the primary survey when it fails to reveal all pathologic glands
  (A) Examination of thymus
  (B) Palpation of retroesophageal space and anterior cervical spine
  (C) Mobilization of superior thyroid pole
  (D) Exploration of carotid sheath.
  (E) Abnormal parathyroid glands located intrathyroidally

Complications of Parathyroid Surgery

- Persistent HPT - 1-20% (experience dependent)
- Temporary - 20%
- Permanent hypocalcemia – 1%
- Nerve injury - recurrent or superior laryngeal - 1-10%
- Bleeding - <5%
Parathyromatosis

- Parathyromatosis, a condition in which hyperfunctioning parathyroid tissue is distributed throughout the neck
- Multiple nodules of hyperfunctioning parathyroid tissue scattered through the neck and mediastinum due to spillage of otherwise benign parathyroid tissue during surgery

How do we know that surgery is successful?

- Intraoperative appearance
- Frozen section
- Drop in intraoperative PTH = 50%
- Ex Vivo radioactivity > 20% of basin

Parathyromatosis.

(A) Early sestamibi image shows physiologic uptake in the thyroid gland (arrow) and salivary glands (arrowhead), and several other foci scattered through the neck. (B) Late sestamibi image confirms that many of these additional foci (arrows) are rests of hyperfunctioning parathyroid tissue. (C) Axial contrast-enhanced CT image shows multiple nonspecific briskly enhancing nodules (arrow), which correspond to the increased sestamibi uptake on fused SPECT-CT (D and E).
Cryopreservation

- Cryopreservation of parathyroid tissue is an alternate technique developed to treat patients with permanent hypoparathyroidism
- This method allows for parathyroid tissue to be stored and then autotransplanted in a delayed fashion once permanent hypoparathyroidism is confirmed
- Permanent hypoparathyroidism is defined as persistent hypocalcemia requiring calcium and vitamin D supplementation 6 months after surgery
- The parathyroid tissue removed during surgery is dissected into 30 to 40 pieces of 1 × 1 × 1 mm. The pieces are then placed into a sterile vial containing ice-chilled saline. The vial is then transported. The supernatant is decanted; about 10 tissue fragments are transferred into each sterile freezing vial to be resuspended in the freezing media.
- Freezing

Questions you will be asked

- Embryology of PTH glands
- Localization techniques for primary hyperparathyroidism (PTH)
- Survey order and location for parathyroid exploration - Where to look when you can't find a PTH gland (first time and redo)
- Question about redo parathyroidectomy