Secondary and Familial Hyperparathyroidism

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Secondary Hyperparathyroidism

- Occurs in setting of CRF
- Chronic overstimulation of parathyroid glands
  - Hyperphosphatemia causes decrease in Ca
  - Decreased renal production of 1,25 dihydroxy vitamin D$_3$ causes reduced intestinal absorption of calcium
  - Decreased Vitamin D Receptor (VDR) levels
  - Reduced Calcium Sensing Receptor (CaSR) levels
- Increase in synthesis and secretion of PTH

Secondary Hyperparathyroidism

- Sequelae include:
  - Increased Ca mobilization from bone
    - Bone and joint pain
    - Weakness
    - Fractures
    - Soft tissue calcification
    - Pruritus
    - Calciphylaxis (medial arterial calcification)
  - Risk of vascular disease and cardiac events
  - Hypercalcemia

Tertiary Hyperparathyroidism

- Follows long-standing Secondary HPTH
- Alteration of set point of PTH cells to feedback inhibition to ionized calcium
- Can present as:
  - Persistent HPTH despite renal transplant
  - New refractory hypercalcemia in patient with previously stable secondary HPTH
Secondary Hyperparathyroidism
Medical management

- P binders
- Diet restriction
- Dialysis (P removal)

Calcimimetics

CaSR expression ↓ [Ca^{2+}] sensitivity ↓
VDR expression ↓
Calcitriol synthesis ↓
Active vitamin D analogues
P management
Direct injection of vitamin D

Ogata et al., 2006

Vitamin D Compounds

1st Generation

2nd Generation
- Side Chain Modifications

3rd Generation
- A-Ring Modifications

Hudson, 2006
Secondary Hyperparathyroidism
Medical management

Cinacalcet RX Sensipar (Amgen)
Calcimimetic agent that acts on the CaSR of the parathyroid chief cell to increase sensitivity to calcium, thereby reducing PTH secretion

Cinacalcet

- Pharma-18 week trial in 71 hemodialysis patients with secondary HPT
- Also received vitamin D therapy and phosphate binders
- Cinacalcet HCl reduced circulating PTH by 32 percent more than control
- Cinacalcet reduced calcium-phosphorus product 7.9 percent over control
- In March 2004, Amgen received FDA approval for the compound to be sold as a treatment for secondary HPT and is approved as Sensipar (as Mimpara in Europe)

Cinacalcet

- FDA approved after NKF-K/DOQI guidelines published
- In clinical trials, Cinacalcet significantly reduced PTH and Ca x P product, regardless of the severity of secondary HPTH
- 3 year efficacy shown
- Long-term toxicity not known
- Data regarding bone, vascular and cardiac benefits, and effect on survival not known yet.
Surgery for Secondary HPTH

- Rate of parathyroidectomy in ESRD patients 7.16/1000 person-years at risk
- Higher rates among younger, female, non-diabetic, peritoneal dialysis patients
- Rates of surgery lower in US than other developed countries

Surgery for Secondary Hyperparathyroidism

- Jofre et al. followed 158 pts for >5 yrs
  - PTH, Ca, PO4, Alk Phos fell significantly compared to matched controls
  - Effects durable >5 yrs
  - Recurrence in 22%
  - One post-operative death

Surgery for secondary HPTH

- United States Renal Database System:
  - 4558 parathyroidectomies in ESRD pts
  - 4558 matched controls
  - 30 day mortality 3.1% vs 1.2%
  - Long term RR of death after parathyroidectomy 15% lower than controls

Secondary Hyperparathyroidism

Indications for Surgery

- National Kidney Foundation K/DOQI guidelines:
  - Severe secondary HPTH with hypercalcemia, hyperphosphatemia refractory to medical treatment
  - Secondary HPTH associated with vascular calcification and cardiovascular disease
Surgery for Secondary Hyperparathyroidism

- Pre-operative localization studies are not necessary
- Bilateral exploration is necessary

Surgery for Secondary Hyperparathyroidism

- Removal of the superior horns of the thymus should be done
- Intrathymic parathyroid tissue present in 15-20% of ESRD patients

Surgery for Secondary Hyperparathyroidism

- Surgical Options:
  - 3 1/2 gland (subtotal) parathyroidectomy
  - Total parathyroidectomy with autotransplantation
  - Total parathyroidectomy without transplantation

Surgery for Secondary Hyperparathyroidism

- Total parathyroidectomy
  - Effective control of HPTH
  - Significant post-operative hypocalcemia
  - Most nephrologists prefer subtotal or AT
- 3 1/2 gland (subtotal) parathyroidectomy
  - Effective immediate control of HPTH
  - Less post-operative hypocalcemia
  - 20% require reoperation
  - Preferred in patients who do not have tertiary HPTH and anticipate renal transplantation in next 1-2 years
Surgery for Secondary Hyperparathyroidism

- 3 1/2 gland (subtotal) parathyroidectomy
  - Prepare patient for both options
  - Identify glands and perform thymectomy first
  - Then choose gland for partial parathyroidectomy
  - Make sure 75-100 mg remnant is viable before removing the other three glands
  - Mark the remaining gland
  - Save fragments of one parathyroid for viable cryopreservation

- Total parathyroidectomy with autotransplant
  - Protect excised parathyroid tissue from OR mishap
  - Place in saline on ice
  - Mince the most normal appearing gland into 1x2 mm fragments
  - Transplant into individual muscle pockets in the non-dominant forearm muscle
  - Mark pockets with non-absorbable suture
  - Other sites (neck, chest wall, abdomen) may be used
  - Viable cryopreservation of some remaining parathyroid tissue
  - Intra-operative PTH

Re-operation for Intra-thyroidal parathyroid in secondary HPTH

Secondary hyperparathyroidism-Treatment by Direct Injection as an alternative to Parathyroidectomy

- Ultrasound-guided percutaneous ethanol ablation of enlarged parathyroids
  - Repeated injections reduced gland size, blood flow
  - Reported incidence of RLN injury
- Ultrasound-guided percutaneous injection of active Vitamin D analogs
  - Suppress PTH secretion
  - Upregulated VDR
  - Induce apoptosis
  - Repeated injections necessary
Familial Hyperparathyroidism

- MEN 1 Syndrome (MENIN)
- MEN2A Syndrome (RET)
- Hyperparathyroidism-Jaw Tumor syndrome (HPRT2)
- Familial Isolated Hyperparathyroidism
- Familial Hypocalciuric Hypercalcemia (Calcium-sensing receptor gene)

Hyperparathyroidism-Jaw Tumor Syndrome

- Parathyroid adenomas—single or multiple
- Adenomas often cystic
- Tendency to recur
- Parathyroid Carcinoma
- Fibro-osseous tumors of the jaw and mandible
- HRPT2 gene

Familial Hypocalciuric Hypercalcemia (FHH)

- Also called Familial Benign Hypercalcemia (FBH)
- Uncomplicated mild hypercalcemia
- Low (<100) 24 hr urine calcium
- Patients do not need surgery!
- Urine calcium/creatinine clearance ratio <0.05
- Mutations in the Calcium-sensing receptor gene

Multiple Endocrine Neoplasia types 1 and 2

- MEN 1
  - Anterior pituitary
  - Parathyroid
- MEN 2
  - Thyroid C-cells
  - Parathyroid
  - Adrenal cortex
  - Pancreatic islets
  - Adrenal medulla
  - Mutations in MEN1, chr 11
  - Mutations in RET, chr 10
Multiple Endocrine Neoplasia Type 1

- Adenomas of the anterior pituitary
- Neuroendocrine tumors of pancreas and duodenum
- Parathyroid hyperplasia
  - Carcinoid tumors
    - 70% are foregut, esp. bronchial and thymus
    - 90% of thymic carcinoids are malignant
  - Lipomas
  - Thyroid nodules
  - Adrenocortical nodules
  - Ependymomas
  - Cutaneous angiofibromas

(Menegotto, KJ, Moreno, AJ. NEJM 1998 26: 1602)

MEN-1 Lesions and their Penetrance

- Parathyroid tumors >95%
- Pancreatic islet tumors >40%
- Ant. Pituitary tumors >30%

MEN-1: Epidemiology

- Prevalence of 2-10 per 100,000
- 1%-18% of patients with primary HPT have MEN-1
- ~20% of patients with ZES have MEN-1
- High penetrance:
  - >50% by age 20
  - >90% by age 40
- 30-40% deaths from MEN1-associated malignancies
- Overall mortality have decreased
- Average age of death:
  - 55 in males
  - 47 in females

(Menegotto, KJ, Moreno, AJ. European Journal of Endocrinology 2003 149:577-582)

MEN-1: Screening

- Clinical Diagnosis: neoplasia of 2 or more MEN-1 related glands
- Familial MEN-1: one member with MEN-1, one 1st degree relative with one feature
- Genetic
- Screening (early & yearly):
  - Biochemical
    - Serum calcium, prolactin
    - GI hormones (gastrin, insulin, etc.)
  - Symptoms:
    - Nephrolithiasis
    - Peptic ulcer disease
    - Neuroglicopenia
    - Hypopituitarism
    - Galactorrhea, amenorrhea in women
    - Acromegaly
    - Cushing’s disease
    - Visual field loss
    - Subcutaneous lipomas

(Carling, T. Curr Opin Oncol 2004 17: 7-12)
**MEN-1: Genetics**

- Autosomal dominant inheritance
- High penetrance, variable expressivity
- Ubiquitously expressed
- Tumor suppressor gene discovered by positional cloning in 1997
- Gene encodes a 610-amino acid protein product, *menin* with unknown function
- Menin is likely a nuclear protein that interacts with the transcription factor *JunD*
- Found in ~80% of MEN-1 patients

**Germline Mutations in the MEN1 Gene**

- Men1 gene: tumor suppressor gene that spans 9kb on chromosome 11q3, consists of 10 exons
- Deletion, frameshift, nonsense, missense, RNA splicing defects that result in loss-of-function
- Mutations seen throughout the entire gene
- No significant homology to other known proteins or superfamilies in database

**Parathyroid Hyperplasia in MEN 1**

- Primary hyperparathyroidism >95% MEN1 patients
- Average onset of hypercalcemia = 25 years of age
- First manifestation of MEN1 >85% patients
- Multiglandular disease, ectopic, supernumerary glands

**Parathyroid Surgery in MEN-1**

- Surgery remains the primary treatment
  - Total 4-gland parathyroidectomy with autotransplantation
  - 3 ½ gland parathyroidectomy
- Increased persistent postop HPT
  - 20%-60% with inexperienced surgeons
  - 0%-25% with experienced surgeons
- Increased postop recurrent HPT (50% by 12 yrs)
Parathyroid Hyperplasia: Gross

- 3 1/2 glands removed (only 1/2 gland at the lower left is present)

MEN 1 Parathyroid Hyperplasia

Parathyroid Hyperplasia: Histology

- Normal parathyroid gland
- Adipose tissue cells are mixed with the parathyroid tissue

- Parathyroid hyperplasia
- Little or no adipose tissue, but any or all cell types normally found in parathyroid are present.

50 yo MEN s/p failed parathyroidectomy with mediastinal adenoma- Trans-cervical thymectomy
MEN 2A presenting at age 67