Advances in Pituitary

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Harvard Medical School
Pituitary tumor types

- Thyrotroph (1%)
  Hyperthyroidism

- Corticotroph (10-15%)
  Cushings Disease

- Somatotroph (10-20%)
  Acromegaly

- Gonadotroph (15-40%)
  “Clinically nonfunctioning”
  Visual field loss
  Hypopituitarism

- Lactotroph (40-50%)
  Hyperprolactinemia

- “Clinically nonfunctioning”

- Hypopituitarism

- Visual field loss

- Acromegaly

- Hyperprolactinemia
Hyperprolactinemia due to psychotropic medications

- Every antipsychotic blocks $D_2$
- Increasingly common; use extends to headaches, mood stabilization, ADHD, depression
- Prolactin elevation (> 72%)
- Atypical neuroleptics such as Risperdal can cause PRL > 100ng/ml
- Elevations more common in women than men
- Symptoms usually don’t occur and do not correlate with prolactin levels
Antipsychotic agents

- Drugs which increase prolactin (PRL) levels
  - Typical Antipsychotics
    - Chlorpromazine (Thorazine®)
    - Haloperidol (Haldol®)
  - Risperidone (Risperdal®)
    - Prolactin sometimes > 200 ng/mL
  - Molindone (Moban®)

- Drugs which increase PRL levels much less often
  - Olanzapine (Zyprexa®)
  - Quetiapine (Seroquel®)
  - Clozapine (Clozaril®)
  - Aripiprazole (Abilify®) partial dopamine agonist
  - Ziprasidone (Geodone®)
Permanent remission of hyperprolactinemia

- About 20-25% of patients may remain normoprolactinemic when dopamine agonists are stopped.
- Withdrawal of cabergoline if prolactin levels normal, MRI no tumor or 50 percent reduction (>5mm from chiasm) and no cavernous sinus invasion.
- Highest recurrence in macroadenomas and micros with visible tumor on withdrawal.
- After 1-2 years of dopamine agonist treatment, doses may be tapered and PRL levels monitored carefully to determine if permanent remission of hyperprolactinemia has occurred and if tumor size is permanent. Monitor carefully for recurrence.
Cystic prolactinoma

Preop imaging with and without contrast; large cystic mass
Prolactinoma: postop

Intraop imaging: cyst is collapsed
Do cystic prolactinomas shrink with DAs?

- 30 pts with cystic (>50% tumor volume)
- 7/30 immediate surgery to decompress chiasm
- 23/30 received Dopamine agonists
  - 16 macro/ 7 micro
  - Cyst reduction in 18/22 (one variable); volume decreased 83.5%
- Can consider a trial *if no visual field loss in selected cases*

Faje et al. 2016 J Clin Endocrinol Metab
Familial isolated pituitary adenomas

20% of FIPA due to aryl hydrocarbon interacting protein (AIP) 11q13.3, which predisposes to adenoma

Daly AF et al J Clin Endocrinol Metab 2007
Daly AF et al J Clin Endocrinol Metab 2010
Tichomirowa M et al Eur J Endocrinol 2011
W.W. de Herder (personal collection)
Long-term mortality with normal IGF-1 Levels after surgery

Cox model predicted survival

Years after surgery

0 5 10 15 20

Normal IGF-1
Elevated IGF-1

Patient in remission
Patient not in remission

Swearingen B et al J Clin Endocrinol Metab 1998
Options for medical therapy

- Dopamine agonists- cabergoline (may need up to 3.5 mg/week)
  
  Most effective in patients with mild IGF-1 elevations

- Somatostatin analogs
  - octreotide
  - lanreotide
  - pasireotide

- GH receptor (GHR) antagonists
  - pegvisomant

Adapted from Melmed et al
# Somatostatin analogue (SSA) therapy

<table>
<thead>
<tr>
<th><strong>Octreotide</strong></th>
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<tbody>
<tr>
<td>– LAR IM</td>
<td>10, 20, 30, 40 mg/month</td>
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<tr>
<td>– OCT SC</td>
<td>100-500 μg TID</td>
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**Lanreotide** (deep subcut)

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<tr>
<td>– Autogel</td>
<td>60, 90,120 mg/month (up to Q 8 weeks)</td>
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<tr>
<td>– SR</td>
<td>30 mg Q 7-14 days (not available in US)</td>
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**Pasireotide** IM

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<tbody>
<tr>
<td>20, 40, 60 mg/month</td>
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</table>
SSA therapy: Efficacy

- Controls GH or IGF-I in 50-66% 
  - but studies vary greatly: 20%-80% depending on patients and study design
- When used as secondary therapy, tumor shrinkage occurs in about 30% of patients
- Tumor shrinkage in most patients is between 20% and 50%

Freda P J Clin Endocrinol Metab 2002
Melmed S et al Pituitary 2010
Abu Dabrh et al J Clin Endocrinol Metab 2014
Prevalence of normal IGF-1 and GH<2.5: Pasireotide LAR vs Octreotide LAR

Colao A et al J Clin Endocrinol Metab 2014
## Pasireotide LAR vs. Octreotide LAR: safety during 12 months

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pasireotide 40 mg (n=63)</th>
<th>Pasireotide 60mg (n=62)</th>
<th>Octreotide 20-30 mg (n=66)</th>
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</thead>
<tbody>
<tr>
<td>Hyperglycemia related</td>
<td>67%</td>
<td>61%</td>
<td>20%</td>
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<tr>
<td>Diarrhea related</td>
<td>16%</td>
<td>19%</td>
<td>5%</td>
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</tbody>
</table>

Colao A et al. J Clin Endocrinol Metab 2014
Supplied as

- 10, 15, 20, 25, 30 mg SC daily
- Evidence for efficacy of bi-weekly use
Pegvisomant: effect on tumor size

• N = 61 on pegvisomant 5-30 mg/day
  – 3 tumors with significant increase
  – All tumor growth in 1st year
  – All were assoc with DC of SSA
  – None were assoc with symptoms

• N = 936 from global surveillance study
  – 3.2 % had significant increase by MRI at mean of 2 year follow up (in subset with central MRI reports)

Buhk J et al J Clin Endocrinol 2010
Van Der Lily AJ et al J Clin Endocrinol Metab 2012
In clinical trials now

- Oral somatostatin analogue
- Somatostatin analogues with reported markedly lower effects on insulin and glucose levels due to different receptor affinities
- Subcutaneous administered analogue
Management of acromegaly: summary points

Goals

– IGF-I normal, OGTT suppression of GH <1 μg/L
– Control tumor

*Surgery remains first-line management*

Medical Therapy

• Dopamine agonists, somatostatin analogs and GH receptor antagonist
• May combine therapies for maximum efficacy

Radiation Therapy: stereotactic or fractionated for uncontrolled tumors or GH/IGF-1, if meds fail, not tolerated or inaccessible
Post surgery if no remission? Expert Consensus Acromegaly Medical Therapy Therapy Guidelines

Consider pasireotide

Adapted from Giustani et al. Nat Endocrinol April 2014
Late night salivary cortisol

How many of you use this test? – please raise your hand if you do

• High sensitivity and specificity (93-100%)
• Especially helpful in early Cushing’s, recurrences
• Normal levels exclude dx in most cases
• Easily performed at home
• Before dental care; avoid hand creams
• Pt chews on cotton, places into tube, mails
• Several samples recommended
• Normal ranges differ widely by lab
• May be high in day/night switch, late pregnancy, other circumstances

Insurance coverage is variable and different for different labs
Late-night salivary cortisol to screen for early-stage recurrence of CD after pituitary surgery

Remission

Recurrence

Sequences: successive measurements of LNSC for each individual patient

Remission

Recurrence

LNSC (nM)

Sequences

LNSC (nM)

Sequences

normal range
Cushing’s surgical failures: repeat transsphenoidal surgery

• Pros (if expert pituitary surgeon)
  − Well tolerated
  − Immediate effect (if successful)
  − Chance for tumor removal and remission

• Cons
  − Higher risk of pituitary hormone deficiencies
  − Risk of recurrent Cushing’s
  − Lower chance of success than 1\textsuperscript{st} surgery (≤75%)
Radiation

- Conventional Fractionated
- Radiosurgery (RS)
  - Single high dose to target
  - Lower dose to other tissue
  - 3 types
    › Linear accelerator (LINAC)
    › Gamma knife
    › Proton beam

No direct comparisons available
- RS may be faster
- For CD, similar cortisol control
Radiation

Overall: Tumor control (83-100%) and Biochemical control (28-86%)

• Pros
  − Well tolerated
  − Single treatment (if radiosurgery)
  − Provides tumor control in most patients
  − Biochemical control in some patients

• Cons
  − Delayed effectiveness (6 months to many years)
  − Medical treatment needed in the interim
  − Long term risks:
    › Pituitary hormone deficiencies/need for replacement
    › Risk to surrounding neurovascular structures
    › Risk of secondary neoplasia
    › Recurrence (rare)

Adrenalectomy for refractory CD

- Immediate resolution of hypercortisolemia
- Requires life-long GC and MC replacement
- Risk of Nelson’s syndrome (CTP)
  - CTP = Corticotroph Tumor Progression
    - 47% CTP by MRI at 7 years (Assié JCEM 2007)
- Complication rates of adrenalectomy: 4-20%
What are the medical treatment options for Cushing’s disease?

**Pituitary gland**
- Cabergoline
- Pasireotide

**Adrenal glands**
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate

GRs on target tissues
- Mifepristone

(* not FDA approved for Cushing’s)
Potential medical targets for Cushing‘s disease

**Rationale:** affinity for receptors on corticotroph adenomas

- cabergoline for dopamine (D2) receptor
- pasireotide for somatostatin (sst5) receptor

\[\downarrow\text{ACTH secretion}\]
Cabergoline in Cushing’s Disease

“Responder” means normal UFC

- 20 Cushing’s disease pts, mean UFC > 2-fold above nl
- 2-year study: 1-7mg/wk cabergoline (median 3.5mg/wk)
- 2 dropouts for “asthenia, hypotension”; adrenal insufficiency?
- Cardiac echos: tricuspid regurg progressed in 1, no change in others
- Similar findings in two other studies; suggests this is an option for CD

(not FDA approved for Cushing’s disease)
73% of patients had at least one hyperglycemia event

N=103

Baseline UFC
Month 6 UFC ≤ ULN

Colao NEJM 2012
What are the treatment options for Cushing’s disease?

Several used for over 50 years
Reduce cortisol by inhibiting adrenal steroidogenesis

ACTH ↑ in pituitary Cushing’s
(? of escape)

Adrenal glands

Ketoconazole *
Metyrapone *
Mitotane *
Etomidate *
LCI699 *

(*) not FDA approved for Cushing’s

GRs on target tissues

Mifepristone

Tissues

Cortisol
Ketoconazole

- Approved for treatment of fungal infections
- Inhibits several enzyme steps in cortisol production
- 4 past studies w/ >15 CD pts: cortisol control 49-99%

**What’s new?**

- Large multicenter, retrospective French study
  - 200 patients on monotherapy at 14 centers over 17y
  - Mean final dose 780mg/d (range 200-1200mg)
  - Control (2 consecutive normal UFCs) in 49%
  - Clinical improvements in DM, HTN, hypokalemia
  - ~20% discontinued for intolerance
    - most common: gastrointestinal, adrenal insuff, pruritis
  - Liver enzyme elevations in 18% (>5XULN, 2.5%)

- Conclusion: effective with acceptable side effects

*(not FDA approved for Cushing’s)* (Castinetti *EJE* 2008 & *JCEM* 2014, Sonino *Clin Endo* 1991, Valassi *Clin Endo* 2012)
Metyrapone

• Inhibits last enzyme step in cortisol synthesis
• Cortisol control reportedly ~75%
  – 3 studies from 1970s to early 1990s (15-53 patients)

What’s new?

• Large multicenter, retrospective UK study (ENDO 2014 oral)
  – 160 patients on metyrapone monotherapy at 13 centers over 16y
  – Control based on cortisol day curve or UFC or am cortisol
  – 74% controlled overall in Cushing‘s syndrome
    (about 2/3rds who took metyrapone over 5m had CD)


(not FDA approved for Cushing’s)
What are the treatment options for Cushing’s disease?

CRH → Pituitary gland → Adrenal glands

Blocks action of cortisol at glucocorticoid receptor (GR)

Doesn’t lower cortisol; ACTH and cortisol ↑ in pituitary Cushing’s

Ketoconazole *
Metyrapone *
Mitotane *
Etomidate *
LCI699 *

(* not FDA approved for Cushing’s)

GRs on target tissues

Mifepristone

Tissues
Mifepristone in Cushing’s Syndrome

- Oral glucocorticoid (GR) antagonist - greater affinity than cortisol or dexamethasone for the receptor
- Also has antiprogestin activity
- Phase 3 clinical trial in 50 patients reported in 2012 → FDA approval for Cushing’s syndrome with hyperglycemia

*Blocks receptor (does not ↓ cortisol) response was assessed clinically*

- Patients had diabetes/impaired glucose tolerance or HTN
- Primary endpoints related to improvements in these disorders
  (25% reduction in AUCgluc on OGTT, 5mmHb reduction in DBP)

(Fleseriu JCEM 2012)
**Decrease in weight**

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<tr>
<th>% Change from baseline (mean ± SE)</th>
<th>D7</th>
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<th>D28</th>
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Baseline 99.5 ± 4.4 kg
n=46

↓ 5.7 ± 1.5%
p<0.001 vs Baseline

"Global Clinical Assessment" of many features, including appearance in photographs, rated by 3 independent reviewers → improved in 88% of patients (p<0.001)

(Fleseriu JCEM 2012, Katznelson Clin Endo 2013)
Mifepristone side effects

- **Adrenal insufficiency**
  - Classified as AI or typical symptoms & treatment with glucocorticoid (dex) in 7
  - *High measured cortisols despite AI may be misleading*

- **Most common** nausea, fatigue, headache

- **Hypokalemia**
  - Common, associated with alkalosis, edema; treated with K & spironolactone
  - Likely due to mineralocorticoid receptor activation from rising cortisol

- **Endometrial Effects**(progesterone receptor blockade)
  - Increased endometrial thickness in half of women
  - 5 cases of vaginal bleeding
  - 3 women had D&C for unresolved endometrial thickening after discontinuation

- **Thyroid** — elevated TSH

- **Lipids** — decreased HDL

*(Fleseriu JCEM ‘12, Endocrine Practice ’13)*

Drug-drug interactions require careful attention
How do we decide which treatment to use?

Consider many factors
Tailor choice to each patient’s individual situation

- Treatment goals
  - biochemical control
  - tumor control
  - severity/urgency (may need to combine meds)
- Other medications (beware drug-drug interactions)
- Medical history/patient factors
- Side effects
- Cost
Cost of treatment

- Transsphenoidal surgery: $50,000-70,000
  - Average LOS 1-2 d
- Adrenalectomy: $75,000-100,000
  - Average LOS 4-8 days
- Proton Radiosurgery: $40,000
  - Outpatient, one day
- Medical – ongoing yearly cost, retail pharmacy
  - Cabergoline: (3.5 mg/wk) - ~$15,000/yr
  - Pasireotide: ~$172,603/ yr
  - Mifepristone: ~ $271,560/ yr at 1200mg dose
Immune checkpoint inhibitors

CTLA-4 (cytotoxic T-lymphocyte antigen-4) and PD-1 (programmed death 1)

Ipi blocks the inhibitory signal to T cells through the CTLA-4 receptor

CTLA-4 is also expressed in the pituitary

Brahmer et al, Cancer Immunol Res 2013
Ipilimumab-associated hypophysitis: pituitary function

Occurs: 12-13% overall* Clinical recognition at MGH since screening started: 15.2%

Hypopituitarism at diagnosis

<table>
<thead>
<tr>
<th>Function</th>
<th>Occurrence</th>
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<tbody>
<tr>
<td>Thyroid</td>
<td>52/56</td>
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<tr>
<td>Adrenal</td>
<td>40/54</td>
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<tr>
<td>Gonadal</td>
<td>42/49</td>
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<tr>
<td>Growth hormone (IGF-1)</td>
<td>6/21</td>
</tr>
<tr>
<td>Prolactin (elevated, low)</td>
<td>2/31, 19/31</td>
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<tr>
<td>Diabetes Insipidus</td>
<td>0/57</td>
</tr>
</tbody>
</table>

Adapted from Faje, Pituitary 2016

Declining TFT values and/or the presence of severe headache and fatigue, hyponatremia, should prompt further investigation with MRI, pituitary function tests

Radiologic course

- Mild to moderate relative diffuse pituitary enlargement in all patients with hypophysitis
  - Chiasm compression did not occur in any patient
  - Enhancement was typically homogenous, though also heterogeneous in some cases
  - Stalk thickening occurred in most but not all cases
  - Pituitary enlargement does not occur without hypophysitis

Pre-Ipi IH

Heterogeneous or Homogeneous enhancement
Ipi-associated hypophysitis: treatment

- No prospective comparison of outcomes in patients treated with high dose glucocorticoids versus physiologic replacement
  - Limited retrospective data suggests that outcomes are not superior in patients receiving high dosages of glucocorticoids (Min, Clin Cancer Res 2015)
  - Of note: melanoma patients with Ipi-associated hypophysitis may have better overall survival (Faje, J Clin Endocrinol Metab 2014; Eatrides, AACR abstract 2014)
Non-hypophysitis endocrinopathies

• **Primary hypothyroidism**
  – 2 patients developed transient mild thyrotoxicosis during treatment with Ipilimumab, followed by primary hypothyroidism

  – 6 patients had newly elevated TSH levels but no preceding results demonstrating thyrotoxicosis (or results suggesting recovery from NTIS)
    • 4/6 had elevated TSH levels and concurrent low FT4
    • 2 patients had mild TSH elevations (6.6 and 6.8), but FT4 levels were not measured

• **Primary adrenal insufficiency** was not diagnosed in any patient in the cohort
Conclusions

- Immune checkpoint inhibitors will likely assume an increasing role in the treatment of various malignancies
- The incidence of endocrine immune related adverse events varies according to the class of agent utilized and their presence including hypophysitis, may predict improved overall survival
- Male gender and older age appear to be risk factors for the development of Ipilimumab-induced hypophysitis
MGH Neuroendocrine Center

• Endocrinology
  – Anne Klibanski
  – Beverly MK Biller
  – Steve Grinspoon
  – Karen Miller
  – Lisa Nachtigall
  – Nicholas Tritos
  – Janet Lo
  – Elizabeth Lawson
  – Pouneh Fazeli
  – Markella Zanni
  – Alex Faje
  – Melanie Shorr
  – Laura Dichtel

• Neurosurgery
  – Brooke Swearingen

• Radiation Oncology
  – Jay Loeffler
  – Helen Shih

• Pediatric Endo
  – Madhusmita Misra

• Endocrine nursing
  – Michelle Gurel
  – Karen Liebert