ACROMEGALY

ETIOLOGY
- Pituitary adenoma >98%
- Ectopic GHRH
- Ectopic GH
- Exogenous GH (?)
ACROMEGALY: EPIDEMIOLOGY

- Sex frequency equal
- Annual incidence: 3-4/million
- Age at diagnosis: Women 45Y, Men 40Y
- Age at death: ~60 years
- Morbidity: cardiovascular, HTN, DM, osteoarthritis, sleep apnea
- Mortality: 2-3 times expected (primarily vascular and respiratory)

ACROMEGALY: MORTALITY

<table>
<thead>
<tr>
<th>Study</th>
<th>DEATHS(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bengtsson 1988</td>
<td>62(37)</td>
</tr>
<tr>
<td>(n=166,1958-1984)</td>
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</tr>
<tr>
<td>Ayuk 2004</td>
<td>95(23)</td>
</tr>
<tr>
<td>(n=419, ?-2001)</td>
<td></td>
</tr>
</tbody>
</table>

ACROMEGALY: ENDOCRINE MANIFESTATIONS*

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acral &amp; soft tissue overgrowth</td>
<td>100</td>
</tr>
<tr>
<td>Hyperhidrosis, hypermetabolism, fatigue, wt gain, paresthesias and joint pain</td>
<td>65-85</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>60</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>46</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>13</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>13</td>
</tr>
<tr>
<td>Hypoadrenalism</td>
<td>4</td>
</tr>
<tr>
<td>Glucose intolerance/hyperinsulinism</td>
<td>50/70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MANIFESTATIONS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>65</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>20</td>
</tr>
<tr>
<td>Sellar enlargement</td>
<td>90</td>
</tr>
</tbody>
</table>
ACROMEGALY: DIAGNOSIS

- **DX**
  - Failure to suppress GH to < 1 ng/ml after oral glucose (75G)
  - Elevated IGF-I (age/sex adjusted)*

- **LOCALIZATION**
  - Pituitary MRI**

*Normal values and assay reliability vary greatly, current automated assays are unreliable
**If MRI negative or consistent with hyperplasia measure GHRH and consider ectopic source of GHRH or GH

ACROMEGALY CRITERIA FOR REMISSION

- Basal or suppressed GH level < 1 ng/ml
- Normal IGF-I level (age/sex adjusted)
ACROMEGALY MANAGEMENT GOALS

- Surgically resect or debulk adenoma
- Normalize GH and IGF-I levels
- Preserve normal pituitary function
- Prevent recurrence, morbidity and mortality

ACROMEGALY: THERAPY

- Transsphenoidal Surgery
- Medical Therapy
  - Dopamine agonists
  - Somatostatin analogs
  - GH receptor antagonist
  - Combination therapy
- Radiotherapy
  - Conventional
  - Stereotactic radiosurgery

ACROMEGALY: TRANSSPHENOIDAL SURGERY

- Response time: immediate
- Success rate: 50%-75% and varies with the surgeon
- Complications in <5% (including Hyopit)
- Remission rates are lower with larger tumors and higher GH levels
ACROMEGALY: IMMEDIATE SURGICAL OUTCOME

<table>
<thead>
<tr>
<th>Remission</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF *</td>
<td>193/254</td>
</tr>
<tr>
<td>1974-1992</td>
<td></td>
</tr>
<tr>
<td>MGH **</td>
<td>92/162</td>
</tr>
<tr>
<td>1978-1996</td>
<td></td>
</tr>
</tbody>
</table>

* JCEM 83:3411,1998
** JCEM 83:3419,1998

ACROMEGALY: STATUS AT LATEST FOLLOW-UP

<table>
<thead>
<tr>
<th>Remission</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF **</td>
<td>162(88.5)</td>
</tr>
<tr>
<td>Persisting active disease</td>
<td>14(7.6)</td>
</tr>
<tr>
<td>Recurrent active disease</td>
<td>7(3.8)</td>
</tr>
<tr>
<td>Total</td>
<td>183(100)</td>
</tr>
</tbody>
</table>

*based on GH level
**JCEM 83:3411,1998

ACROMEGALY MEDICAL THERAPY*

- DOPAMINE AGONISTS
- SOMATOSTATIN ANALOGS
- GH RECEPTOR ANTAGONIST
- COMBINATIONS

* In general the best responses occur in those with the lowest baseline GH and IGF-I levels
### ACROMEGALY

**DOPAMINE AGONISTS**
- Bromocriptine - not effective
- Cabergoline
  - Normal GH/IGF-I in 20-40%
  - Not effective in reducing tumor size

### ACROMEGALY

**SOMATOSTATIN ANALOGS (SSA)**
- Octreotide LAR 20-40 MG IM monthly
- Lanreotide Autogel 60-120 MG SQ monthly
  - GH or IGF-I normal in 40-70%
  - Tumor size reduction in ~37%*
    (range 23-73% of patients)
  - GI side effects in 10-20%
  - *JCEM 90:4405, 2005 (N=424)

### ACROMEGALY

**SOMATOSTATIN ANALOGS**

<table>
<thead>
<tr>
<th></th>
<th>GH&lt;2.5</th>
<th>IGF-I=N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide LAR*</td>
<td>57(%)</td>
<td>67(%)</td>
</tr>
<tr>
<td>Lanreotide ATG**</td>
<td>54(%)</td>
<td>59(%)</td>
</tr>
</tbody>
</table>

*JCEM 99:4465, 2008 (n=612). **Pituitary July 2009 (n=99, 43% with normal GH+ IGF-I)
ACROMEGALY

- PEGVISOMANT
  - GH receptor antagonist
  - Dose: 10-40 MG SQ daily
  - Dose req't higher in women, with >wt. and higher IGF-I levels
  - IGF-I levels normal in 56-97% ????
  - GH levels increase
  - Incidence of tumor progression unknown
  - Abnormal LFTS in 20%
  - Expensive

ACROMEGALY

- PEGVISOMANT*

<table>
<thead>
<tr>
<th>Method</th>
<th>IGF-I NORMAL(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIA</td>
<td>** 85 ** 79 **</td>
</tr>
<tr>
<td>ICMA</td>
<td>** 56 ** 62 **</td>
</tr>
</tbody>
</table>

*Clin Endocrinol 71:549,2009
** Pegvisomant alone
*** Pegvisomant plus octreotide LAR
ACROMEGALY

- COMBINATION THERAPY
  - SSA and cabergoline
  - SSA monthly, pegvisomant weekly

ACROMEGALY
RADIATION THERAPY

- CONVENTIONAL

- STEREOTACTIC RADIOSURGERY
  GAMMA KNIFE
ACROMEGALY
RADIATION THERAPY

- CONVENTIONAL
  - Slow response (10+ years)
  - Hypopit in >50%
  - Excess mortality ??

- GAMMA KNIFE
  - Normal GH and IGF-I in ~50%
    at 5 years
  - Hypopit varies with target
  - Prevents tumor growth

ACROMEGALY: CAUSE OF DEATH*

- CAUSE       SMR(P)
  Cerebrovasc. 2.06 (<0.001)
  Cardiovasc.  1.76 (<0.001)
  Respiratory  1.85 (<0.001)
  Cancer       1.16 (NS)
  All cause    1.60 (0.001)

* Orme - JCEM 83:2730,1998 (N=1362)
### ACROMEGALY: MORTALITY

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths</th>
<th>Deaths (%)</th>
</tr>
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<td>95(23)</td>
<td></td>
</tr>
</tbody>
</table>

### AYUK 2004*

- **THERAPY**
  - Surgery alone: 136(32.5)
  - Surgery/radiation: 120(28.7)
  - Radiation alone: 91(21.8)
  - Medical therapy: 71(16.9)

*JCEM 89:1613,2004 (N=419, 52% in remission with GH < 2.0 ng/ml)*

### ACROMEGALY: CAUSE OF DEATH*

<table>
<thead>
<tr>
<th>Cause</th>
<th>SMR</th>
<th>ALL Pts</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovasc.</td>
<td>2.68</td>
<td>4.42</td>
<td></td>
</tr>
<tr>
<td>Cardiovasc.</td>
<td>1.37</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.52</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>0.91</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>1.26</td>
<td>1.58</td>
<td></td>
</tr>
</tbody>
</table>

* Ayuk - JCEM 89:1613,2004 (N=419)
ACROMEGALY
CURRENT MORTALITY

- STUDY          DEATHS
  - UCSF 1998 (n=254)*  29 (11%)
  - MGH 1998 (n=149)**  12 (8%)

*JCEM 83:3411,1998
**JCEM 83:3419,1998

ACROMEGALY CURRENT MORTALITY

<table>
<thead>
<tr>
<th>UCSF</th>
<th>DEATHS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Actual</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMISSION</td>
<td>20.2</td>
<td>19.8</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>PERSISTING DISEASE</td>
<td>9.0</td>
<td>2.9</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

ACROMEGALY: MORTALITY

- META-ANALYSIS*

| Studies | N | Patients | 4806 | Deaths | 1116(23%) |

ACROMEGALY: MORTALITY

<table>
<thead>
<tr>
<th>META-ANALYSIS</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies (N=18, 1970-2007)</td>
<td>1.7</td>
</tr>
<tr>
<td>Mean year of entry prior to 1984</td>
<td>2.2</td>
</tr>
<tr>
<td>Mean year of entry after 1984</td>
<td>1.3</td>
</tr>
<tr>
<td>Remission in &lt; 70%</td>
<td>2.0</td>
</tr>
<tr>
<td>Remission in &gt; 70%</td>
<td>1.2</td>
</tr>
<tr>
<td>SS analog RX in &lt; 30%</td>
<td>2.0</td>
</tr>
<tr>
<td>SS analog RX in &gt; 30%</td>
<td>1.2</td>
</tr>
</tbody>
</table>

ACROMEGALY: MORTALITY

<table>
<thead>
<tr>
<th>META-ANALYSIS*</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final GH &gt; 2.5 ng/ml</td>
<td>1.9</td>
</tr>
<tr>
<td>Final GH &lt; 2.5 ng/ml</td>
<td>1.1</td>
</tr>
<tr>
<td>OGTT GH &gt; 1.0 ng/ml</td>
<td>2.3</td>
</tr>
<tr>
<td>OGTT GH &lt; 1.0 ng/ml</td>
<td>1.2</td>
</tr>
<tr>
<td>IGF-I elevated</td>
<td>2.5</td>
</tr>
<tr>
<td>IGF-I normal</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Eur J Endocrinol 159:89, 2008

ACROMEGALY: CONCLUSIONS

- Surgery is the initial therapy of choice
- Patients with persisting or recurrent disease should be treated with medical therapy (SSAs, cabergoline and/or pegvisomant)
- With current therapy remission is achieved in >90% of patients
ACROMEGALY: CONCLUSIONS

- Patients in remission have reversal of excess mortality
- Radiation should be reserved for those very few patients who fail medical RX or who have tumor progression
- Interpret IGF-I levels with caution

END

THANK YOU!
PITUITARY LESIONS
ETIOLOGY IN ADULTS
- Pituitary Adenomas (>90%)
- Craniopharyngioma
- Empty Sella Syndrome
- All Others Are Rare (<1%)

PITUITARY ADENOMAS

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>Hypogonadism/Galactorrea</td>
</tr>
<tr>
<td>GH</td>
<td>Acromegaly/Gigantism</td>
</tr>
<tr>
<td>ACTH</td>
<td>Cushing's Disease</td>
</tr>
<tr>
<td>TSH</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>NON-FX</td>
<td>Hypogonadism/Hypopit</td>
</tr>
</tbody>
</table>
PITUITARY ADENOMAS
PRESENTATION

- Early Endocrine Symptoms
  - Hypogonadism (PRL, GH or ACTH excess)
  - Hypersecretion (PRL, GH or ACTH)

- Late Local Symptoms
  - Headache
  - Visual field defects
HYPERPROLACTINEMIA

“Prolactin is the sed rate of the endocrinologist”

Wm Doughaday
CASE NO. 1

- 42 yo woman
- 1996: Infertility
  - PRL 30-40, TSH increased
  - RX'd with T4
- 1998: PRL 29.1 ng/ml (3-19), TSH 2.81
  - IVF - FTND
- 2001: IVF - FTND - twins
- 2002: Amenorrhea, TSH 8.58
  - T4 dose adjusted
- 2005: Amenorrhea continues
  - PRL 83.1, TSH 2.65

NOW WHAT??

42 yo with infertility, mildly elevated prolactin
HYPERPROLACTINEMIA

- Incidence
- Etiology
- When to measure
- Further evaluation

<table>
<thead>
<tr>
<th>HYPERPROLACTINEMIA INCIDENCE</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea Alone</td>
<td>15</td>
</tr>
<tr>
<td>Galactorrhea Alone</td>
<td>30</td>
</tr>
<tr>
<td>Amenorrhea/Galactorrhea</td>
<td>80</td>
</tr>
</tbody>
</table>
HYPERPROLACTINEMIA
ETIOLOGY

1. Physiologic
   - Pregnancy/Postpartum
   - Breast Feeding

2. Miscellaneous
   - Primary Hypothyroidism
   - Idiopathic /Pituitary Hyperplasia
   - Macroprolactinemia
   - Renal Failure
   - Liver Failure

3. Hypothalamic-Pituitary Lesions
4. Drug Induced
5. Neurogenic
MACROPROLACTINEMIA

- "True prolactin" - 23 kDa monomer
- Macroprolactin (Big/Big) -> 100 kDa complex of PRL and anti-PRL Igg antibody
- Prevalence
  - 10% (n=1106, JCEM 87:581, 2002)
  - 22% (n=2089, JCEM 90:3927, 2005)
- PRL levels >90% are <100 ng/ml
- Detection by chromatography or PEG precipitation
MACROPROLACTINEMIA

Clinical Features
- Many have no sx
- Many have*
  - Galactorrhea alone
  - Oligo/amenorrhea alone
  - Infertility alone
  *ie-the reason they were referred
- Very few have
  - Amenorrhea/galactorrhea

When To Assay
- No sx/idiopathic
- Minor sx
- Neg/equivocal MRI

Questions
- Assay all samples??
- Assay all samples with PRL <100 or <200ng/ml??

HYPERPROLACTINEMIA

ETIOLOGY

3. HYPOTHALAMIC-PITUITARY LESIONS
   - Prolactinoma
   - Other Pituitary Adenomas
   - Pituitary Stalk Compression/Section
   - Hypothalamic Lesions
   - Empty Sella Syndrome
HYPERPROLACTINEMIA
ETIOLOGY
4. DRUG INDUCED

- Estrogen/OCP's
- Metoclopramide
- Cimetidine
- Verapamil
- Cocaine
- Narcotics
- Tricyclics
- MAO inhibitors
- Phenothiazines
- Haloperidol
- Resperidone

HYPERPROLACTINEMIA
ETIOLOGY
5. NEUROGENIC

- Breast Stimulation
- Local Breast Disease
- Chest Wall Injury/Trauma
- Spinal Cord Lesions

HYPERPROLACTINEMIA
WHEN TO MEASURE

- Galactorrhea and/or Amenorrhea
- Unexplained Hypogonadism/Infertility in Males
- Suspected Pituitary/Hypothalamic Dysfunction
- Empty Sella Syndrome
HYPERPROLACTINEMIA
FURTHER EVALUATION

- Confirm Elevated Level
- Drug/Medication HX
- Pregnancy Test (Women)
- Testosterone Level (Men)
- Thyroid FX: TSH
- Test For Macroprolactinemia
- MRI

PROLACTINOMAS

- Clinical Features
- Diagnosis
- Therapy
- Questions

PROLACTINOMAS
CLINICAL PRESENTATION

- Galactorrhea
  - Women: ~80%
  - Men: ~10%
- Early Endocrine Symptoms
  - Women: Oligo/Amenorrhea/Infertility
  - Men: Decreased Libido/Infertility
- Late Local Symptoms
  - Headache
  - Visual Field Defect
PROLACTINOMAS
DIAGNOSIS
- Exclude Other Causes
- Persisting Hyperprolactinemia
  
PRL VALUE
  Microadenoma 20-100
  Probable Adenoma 100-200
  Definite Adenoma >200*
- Abnormal MRI**
  *Levels may be higher with pregnancy and resperidone
  **Caution re: false positives

PROLACTINOMAS
THERAPY
- MICROADENOMAS
  - Dopamine Agonists
  - (Transsphenoidal Surgery)
- MACROADENOMAS
  - Dopamine Agonists
  - (Surgery/Dopamine Agonists/Radiotherapy)
PROLACTINOMAS

MEDICAL THERAPY

• Bromocriptine
• Cabergoline

PROLACTINOMAS
BROMOCRIPTINE THERAPY

• Microadenomas
  • PRL or gonadal FX normal in 80-90%
  • PRL normal in 60-70%

• Macroadenomas
  • PRL normal in 50-70%
  • Tumor size reduction in 70% (>25%)

  Molitch and Reichlin 1980
PROLACTINOMAS
BROMOCRIPTINE THERAPY

- ADVANTAGES
  - Non-invasive
  - Reasonable success rates

- DISADVANTAGES
  - Intolerance (5-12%)
  - Resistance (9%)
PROLACTINOMAS
CABERGOLINE THERAPY

- ADVANTAGES
  - More effective and better tolerated than bromocriptine

This is the drug of choice

PROLACTINOMAS: MEDICAL RX QUESTIONS

- Pregnancy ??
- Life long therapy ??
- Cardiac damage ????

PROLACTINOMAS & PREGNANCY

- There is no increased risk of fetal loss or fetal abnormalities when dopamine agonists are used to restore fertility
- Experience is greater with bromocriptine than with cabergoline
### PROLACTINOMAS & PREGNANCY

#### TUMOR ENLARGEMENT PERCENT

- Microadenomas: <2%
- Macroadenomas (untreated): 23%
- Macroadenomas (post-surgery): 3%


---

### PROLACTINOMAS & PREGNANCY: PROTOCOL

- Microadenomas
  - RX with cabergoline until cycles normalize
  - With first missed period obtain HCG
  - If positive D/C RX
  - (Follow prolactin Q 6 weeks)
  - (Follow visual fields)

---

### PROLACTINOMAS & PREGNANCY

- Macroadenomas
  - Prior surgery effectively reduces the risk of tumor expansion
  - There are very limited data on risk after tumor suppression with dopamine agonists
PREGNANCY & PROLACTINOMAS: DATA

- Macroadenomas*
  - Conception with bromocriptine 86
  - VFD during pregnancy 20 (23%)
  - RX'd with surgery 4
  - RX'd with bromocriptine 15
  - Successful outcome 20

- Macroadenomas
  - Continuous bromocriptine** 29
  - VFD during pregnancy 2
  - Successful outcome 29

** Fertil Steril 41:793, 1984
7/29 patients probably had non-functioning adenomas (BC PR=12000g/ml)

PREGNANCY & PROLACTINOMAS

- Macroadenomas: Options
  - Surgery prior to conception
  - D/C cabergoline at conception and follow
  - Suppress tumor with cabergoline for 6-36 months, then D/C at conception and follow
  - (Continuous bromocriptine: there are no data on cabergoline)

PROLACTINOMAS & PREGNANCY

- WORST CASE=TUMOR ENLARGEMENT
  - Usually in 2nd or 3rd trimester with visual defect and headache
  - MRI (non-contrast) to define size
  - Bromocriptine is effective in most (N=15)
  - Cabergoline is also effective (N=1)
  - Deliver early if fetus viable
  - Transsphenoidal surgery as last resort
PROLACTINOMAS

- Is Life Long Therapy Required ??

HYPERPROLACTINEMIA
CABERGOLINE WITHDRAWAL

- Following 2-4 YRS of therapy ~30% can be withdrawn and remain normoprolactinemic
- Best outcomes- 1) NTH, 2) Microadenomas, 3) post therapy PRL<5 and residual tumor <3mm
- CAUTION: current studies are poor and include many patients without adenomas

PROLACTINOMAS
CABERGOLINE WITHDRAWAL

- STRATEGY
  - NTH-RX 1 year and withdraw
  - Micro-RX 3 years and withdraw
  - Macro-RX 3-5 years, reassess PRL level and tumor size and consider withdrawal
PROLACTINOMAS
CARDIAC RISK?

- Patients treated with pergolide or cabergoline for Parkinson's are at increased risk of cardiac valve damage and risk is dose related.
- Average dose of cabergoline was 3.6 mg per day=25.2 mg per week.*

- Usual doses of cabergoline for prolactinomas are 0.25-1.0 mg per week.
  - *NEJM 2007;356:29-38

---

PROLACTINOMAS
CARDIAC RISK?

- STRATEGY
  - Use lowest possible dose
  - Withdraw RX as soon as possible
  - If long term RX is required, baseline and follow up cardiac evaluation should be performed.

---

MANAGEMENT OF NTH

- R/O Macroprolactinemia
- Follow
- Cabergoline
- Gonadal steroid replacement

  - NOTE: Untreated hypogonadal patients may develop osteopenia.
Don't forget the "Hook Effect"

PROLACTINOMAS
ACROMEGALY: MORTALITY

- Rajasoorya 1994 (N=146, 1964-1989) 32(22)
- Ayuk 2004 (N=419, 1990-2001) 95(29)