ACROMEGALY

ETIOLOGY

- Pituitary adenoma >98%
- Ectopic GHRH
- Ectopic GH
- Exogenous GH (?)

EPIDEMIOLOGY

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

CLINICAL MANIFESTATIONS*

<table>
<thead>
<tr>
<th>Condition</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>Oligo/amenorrhea</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>

ACROMEGALY: LOCAL MANIFESTATIONS

PERCENT

- Headache 65
- Visual field defect 20
- Macroadenoma 90

ACROMEGALY: DIAGNOSIS

- DX
  - Failure to suppress GH to < 1ng/ml 1hr after 75G glucose po (IRMA or ICMA assay) OR random GH >15-20ng/ml
  - Elevated IGF-I (age/sex adjusted). Normal values and assay reliability vary greatly. Many current assays are unreliable.
  - Best assay LC/MSMS (Quest)

- LOCALIZATION
  - Pituitary MRI (> 90% are macroadenomas)*

*If MRI negative or consistent with hyperplasia measure GHRH and consider ectopic source of GHRH or GH
ACROMEGALY CRITERIA FOR REMISSION

• Fasting or glucose suppressed* GH level <1 ng/ml AND
• Normal IGF-I level (age/sex adjusted)
• NOTE: Many studies do not follow these criteria

*1 hour post 75G glucose po

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
  • Somatostatin analogs (SSA’s)
  • Dopamine agonists
  • GH receptor antagonist (Pegvisomant)
  • Combination therapy
• Radiotherapy
  • Conventional
  • Stereotactic radiosurgery

Growth Hormone

JCEM 80:2768, 1995
ACROMEGALY: TRANSSPHENOIDAL SURGERY

- Response time: immediate
- Success rate: 50%-75% and varies with the experience of the surgeon
- Complications in <5% (including Hypopit)
- 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 [median preop GH 27ng/ml; median adenoma size 18 mm]
** JCEM 83:3419,1998

ACROMEGALY: STATUS AT LATEST FOLLOW-UP*

<table>
<thead>
<tr>
<th></th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</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*

- SOMATOSTATIN ANALOGS
- DOPAMINE AGONISTS
- PEGVISOMANT (GH receptor antagonist)
- COMBINATIONS

* In general the best responses occur in those with the lowest baseline GH and IGF-I levels. Most pts have had 1 or more prior therapies (Surgery, XRT and/or medical RX)
ACROMEGALY: SOMATOSTATIN ANALOGS (SSA’s)

• OCTREOTIDE (OCT)
  • SQ TID
  • LAR 20-40 mg IM monthly

• LANREOTIDE (LAN)
  • SR 30 mg SQ every 7-14 days
  • Autogel (ATG) 90-120 mg SQ monthly

• PASIREOTIDE (PAS)
  • (200-900 mcg SQ BID)
  • LAR 40-60 mg IM monthly

• GI side effects in 10-45%

ACROMEGALY: SSA’s

• OCT vs LAN*
  GH<2.5 IGF-I=N BOTH
  • OCT LAR (N=75) 65% 47% 36%
  • LAN ATG (N=74) 60% 53% 42%
  *JCEM 93:2957, 2008 (Review of 5 studies)

• OCT LAR vs LAN ATG -- Overall responsiveness to either drug = 31% (GH<2.5 and IGF-1 N)
  **Endocrine Practice Epub Oct 2015
  (N=354, Review of 9 studies)

ACROMEGALY: SSA’s

• OCT VS OCTREOTIDE*
  • 155 pts controlled on injectable SSA’s
  • RX’d with oral Octreotide 40-80 mg/day for 7 months
  • 65% maintained control at 7 months
  *JCEM 100:1699, 2015

ACROMEGALY: SSA’S

<table>
<thead>
<tr>
<th>PAS VS OCT*</th>
<th>PAS LAR</th>
<th>OCT LAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>176</td>
<td>182</td>
</tr>
<tr>
<td>Pre RX GH</td>
<td>21.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Dose (mg/month IM)</td>
<td>40-60</td>
<td>20-30</td>
</tr>
<tr>
<td>GH&lt;2.5/IGF-1 N(%)</td>
<td>31.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Diarrhea(%)</td>
<td>39.3</td>
<td>45.0</td>
</tr>
<tr>
<td>Hyperglycemia(%)</td>
<td>32.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Diabetes(%)</td>
<td>24.2</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*JCEM 99:791, 2014 (no prior medical therapy)
ACROMEGALY: SSA’s TUMOR SHRINKAGE

<table>
<thead>
<tr>
<th>Drug</th>
<th>% WITH DECREASE</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT(SQ/LAR)</td>
<td>39%</td>
<td>23-73%</td>
</tr>
<tr>
<td>LAN(SR/ATG)</td>
<td>33%</td>
<td>5-79%</td>
</tr>
</tbody>
</table>

*JCEM 90:4405,2005 (11 studies, 10 SQ)
**PITUITARY 13:60,2010

NOTE: Both prevent tumor growth

ACROMEGALY: SSA’S TUMOR SHRINKAGE*

<table>
<thead>
<tr>
<th>Drug</th>
<th>% WITH DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS LAR (N=176)</td>
<td>81</td>
</tr>
<tr>
<td>OCT LAR (N=182)</td>
<td>77</td>
</tr>
</tbody>
</table>

*JCEM 99:791,2014 (>20% reduction in tumor volume)

ACROMEGALY: SSA’s PRIMARY THERAPY

- 68 pts treated with OCT LAR 10-30mg monthly for 48 weeks*
- Mean baseline GH 33.6 ± 62.6
- Post RX GH < 2.5ng/ml in 44%
- Post RX IGF-I normal in 34%

*Clin Endocrinol 66:859,2007

ACROMEGALY: SSA’s POST SURGERY*

<table>
<thead>
<tr>
<th>Drug</th>
<th>POST-OP GH</th>
<th>POST SSA GH &lt; 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT LAR (N=36)</td>
<td>8.5 ± 9.2</td>
<td>64%</td>
</tr>
<tr>
<td>LAN ATG (N=32)</td>
<td>7.9 ± 7.0</td>
<td>78%</td>
</tr>
</tbody>
</table>

*Tutuncu et al, Pituitary 15:398,2012 (OCT LAR 20-30mg or LAN ATG 90-120mg monthly for 1.5 years)
### ACROMEGALY: Dopamine Agonists

#### Bromocriptine Alone*
- Median pre RX GH 11.2 ng/ml (6.5-31.8)
- Post Rx GH <2.5 in 15.3% (18/118)
- Post RX IGF-1 normal in 32% (17/53)
- **NOT EFFECTIVE**  
  *JCEM 94: 1255, 2009 (118 pts treated for 1 yr)  
  Median dose 7.5 mg/day

#### Cabergoline Alone*
- 149 pts treated for 2.6-24 months. Mean dose 2.6mg/wk (0.85-7mg/wk)
- Mean PRE RX GH 16ng/ml
- Post RX GH <2.5ng/ml in 48%
- Post RX IGF-I in 34%
- Better responses with lower baseline IGF-I, higher baseline PRL, longer treatment duration and possibly higher dose  
  *JCEM 96:1327,2011 (Meta-analysis of 10 studies)

### ACROMEGALY

#### Pegvisomant (PEG)
- GH receptor antagonist-blocks IGF-I prod’n
- Dose 10-40 MG SQ daily
- Dose req’t higher in women, with >wt. and higher IGF-I levels
- GH levels increase as much as 10-20ng/ml
- Incidence of tumor progression ~3-5%
- Abnormal LFTS in 20%

#### Peg Visomant (PEG)
- 152 pts*, 131 treated for 6 mo, 90 (59%) for 12 mo and 39(26%) for 18 mo
- Pre RX GH 10.2±16
- PEG dose 10-40mg/day (mean 14.7-19.6 in 3 cohorts)
- IGF-I normal in 87/90(97%) of pts treated for 12 mo  
  * Lancet 358:1754,2001
ACROMEGALY: PEG

- 229 pts*, 147 treated for 6 mo, 102 (45%) for 12 mo and 39 (17%) for 24 mo
- Pre RX GH-NA
- PEG dose 10-30mg/day (16.5±7.7)
- IGF-I normal in 64% at 6 mo, 71% at 12 mo and 76% at 24 mo
  *Eur J Endocrinol 156:75, 2007

ACROMEGALY: PEG*

- 792 pts treated for a mean of 3.31 years
- Pre RX GH-NA
- PEG dose 14.3-20mg/day
- IGF-I normal in 62% at 1 year and did not improve further in years 2-5
  *Eur J Endocrinol 161:S19, 2009

ACROMEGALY

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

ACROMEGALY: SSA’s AND CABERGOLINE*

- 77 pts treated for 6.6±4.1 mo (2-20). Mean CAB dose 2.5mg/wk, LAN SR 30mg/10days (N=16) or OCT LAR 30mg/28 days (N=61)
- Mean pre RX GH 7.4ng/ml
- Post RX GH <2.5ng/ml AND IGF-I normal in 52%
  *JCEM 96:1367, 2011 (Meta-analysis of 5 studies)
ACROMEGALY: SSA’s AND PEG*

- 57 pts treated for 28 wks with LAN ATG 120mg/mo and PEG 40-120mg/wk
- Pre RX GH-NA
- Post RX IGF-I normal in 58%

*Eur J Endocrinol 164:325,2011

ACROMEGALY: RADIATION THERAPY*

- CONVENTIONAL
  - Slow response (10+ years)
  - <50% in remission at 5 years, 47-76% at 10 years
  - Excess mortality?
- GAMMA KNIFE
  - Normal GH and IGF-I in ~50% at 12-60 months
  - Hypopituitarism varies with the target

*Pituitary 12:3,2009 - Both prevent tumor progression

ACROMEGALY MORTALITY 1998

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>SMR(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause</td>
<td>1.60 (0.001)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>2.06 (&lt;0.001)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.76 (&lt;0.001)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.85 (&lt;0.001)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.16 (NS)</td>
</tr>
</tbody>
</table>

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

ACROMEGALY MORTALITY 1998

<table>
<thead>
<tr>
<th></th>
<th>DEATHS</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients(254)</td>
<td>29(11%)</td>
<td>1.3</td>
</tr>
<tr>
<td>Remission</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Persisting disease</td>
<td>9</td>
<td>3.1</td>
</tr>
<tr>
<td>MGH**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients(149)</td>
<td>12(8%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Remission</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Persisting disease</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

ACROMEGALY MORTALITY 2004

DEATHS(%)  
• Holdaway 2004  
(n=208,1964-2000)  
72(35)  
• Ayuk 2004  
(n=419, ?-2001)  
95(23)

ACROMEGALY MORTALITY  
AYUK 2004*

• THERAPY  
N(%)  
Surgery alone  
136(32.5)  
Surgery/radiation  
120(28.7)  
Radiation alone  
91(21.8)  
Medical therapy alone  
71(16.9)

*JCEM 89:1613,2004 (N=419, 61% had surgery, 51% had radiation and only 52% were in remission with GH < 2.0 ng/ml)

ACROMEGALY:MORTALITY  
AYUK 2004*

SMR

• CAUSE  
SMR  
ALL PTS  
XRT  
Cerebrovasc.  
2.68  
4.42  
Cardiovasc.  
1.37  
1.60  
Respiratory  
1.52  
1.75  
Cancer  
0.91  
1.00  
All cause  
1.26  
1.58  
* JCEM 89:1613,2004(N=419)

ACROMEGALY:MORTALITY  
META-ANALYSIS*

SMR

• All studies  
1.7  
• Before 1984,Remission in<70%, SSA RX in<30%,Final GH>2.5,OGTT GH>1ng/ml, IGF-1 elevated  
1.9-2.5  
• After 1984,Remission in >70%, SSA RX in >30%, Final GH<2.5ng/ml, OGTT GH<1ng/ml, IGF-1 normal  
1.1-1.3

ACROMEGALY: CONCLUSIONS

- Surgery is the initial therapy of choice
- Patients with persisting or recurrent disease should be treated aggressively with medical therapy (SSA’s, cabergoline and/or pegvisomant)
- With current therapy remission can be achieved in >90% of patients
- Patients in remission have reversal of excess mortality

ACROMEGALY: SSA’s

<table>
<thead>
<tr>
<th>Method</th>
<th>GH&lt;2.5</th>
<th>IGF-I-N</th>
<th>BOTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT LAR (N=612)*</td>
<td>57%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>LAN SR (N=914)*</td>
<td>48%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>LAN ATG (N=99)**</td>
<td>54%</td>
<td>59%</td>
<td>43%</td>
</tr>
</tbody>
</table>

*JCEM 90:4465,2005
**Pituitary 13:18,2009

ACROMEGALY RADIATION THERAPY

- CONVENTIONAL
- STEREOTACTIC RADIOSURGERY
  - Gamma Knife
  - Both prevent tumor progression
ACROMEGALY: CONCLUSIONS

- Patients in remission have reversal of excess mortality
- Radiation should be reserved for those few patients who fail medical RX or who have tumor progression

ACROMEGALY: MORTALITY

- META-ANALYSIS*
  - N
  - Studies 18
  - Patients 4806
  - Deaths 1116 (23%)


ACROMEGALY: MORTALITY

- META-ANALYSIS
  - All studies (N=18, 1970-2007) SMR 1.7
  - Mean year of entry prior to 1984 2.2
  - Mean year of entry after 1984 1.3
  - Remission in < 70% 2.0
  - Remission in > 70% 1.2
  - SS analog RX in < 30% 2.0
  - SS analog RX in >30% 1.2

ACROMEGALY: MORTALITY

- META-ANALYSIS*
  - Final GH > 2.5 ng/ml SMR 1.9
  - Final GH < 2.5 ng/ml 1.1
  - OGGT GH >1.0 ng/ml 2.3
  - OGGT GH <1.0 ng/ml 1.2
  - IGF-I elevated 2.5
  - IGF-I normal 1.1

*Eur J Endocrinol 159:89, 2008
ACROMEGALY: MORTALITY

- Bengtsson 1988
  (n=166,1958-1984)  62(37)
- Holdaway 2004
  (n=208,1964-2000)  72(35)
- Ayuk 2004
  (n=419, ?-2001)  95(23)

ACROMEGALY: CURRENT MORTALITY

<table>
<thead>
<tr>
<th>MGH*</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL (N=149)</td>
<td>1.16</td>
</tr>
<tr>
<td>SURG REMISSION</td>
<td>0.84</td>
</tr>
<tr>
<td>PERSISTING DISEASE</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*JCEM 83:3419,1998

ACROMEGALY CURRENT MORTALITY

<table>
<thead>
<tr>
<th>UCSF*</th>
<th>DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual</td>
</tr>
<tr>
<td>REMISSION</td>
<td>20.2</td>
</tr>
<tr>
<td>PERSISTING DISEASE</td>
<td>9.0</td>
</tr>
</tbody>
</table>

*JCEM 83:3411,1998
ACROMEGALY
CURRENT MORTALITY

• STUDY          DEATHS  SMR
  – UCSF 1998 (n=254)*  29 (11%)  1.30
  – MGH 1998 (n=149) **  12 (8%)  1.16

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

ACROMEGALY: CONCLUSIONS

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