Acromegaly: 25 years of Growth

Lewis S. Blevins Jr., M.D.

California Center for Pituitary Disorders at UCSF
providing state-of-the-art treatment and world-class care
Acromegaly: 25 years of Growth

Onset of Acromegaly ~ 25 yrs ago
  Profound changes in appearance
  Medical problems

My first patient with GH excess ~ 25 yrs ago
  oGTT
  oGTT cutoffs evolved
  IGF-1 assays

Computed Tomography
  dynamic enhanced MRI

Conventional XRT
  Stereotactic

Bromocriptine
  Sandostatin sc 1992
  Cabergoline 1996-1997
  Sandostatin LAR 1999
  Pegvisomant 2003
  Lanreotide 2008
  Pasireotide ?

Molecular pathogenesis
  Mortality data defining remission

We are witnessing an evolution in the treated natural history of the disease!
Cushing’s monsters

James H. Buchanan, PhD

‘Nature knows no differences but rather believes that all is beautiful, all is sublime and precious that is its own. It is we humans who speak of gods and monsters, of mis-formed and well-formed, of beauty and ugliness. Nature knows nothing of this.’

Rondo Hatton starred in “The Pearl of Death” And “The House of Horrors.”
Charles Byrne
The Irish Giant 8’4”

AIP mutation
Acromegaly

Prognathism and separation of the mandibular teeth
Acromegaly

Acral enlargement
CTS with thenar wasting
Arthropathy
Acromegaly

Toxic MNG due to Acromegaly and a 2 cm GH secreting adenoma

Diffuse goiter due to a combined GH and TSH-secreting adenoma
Acromegaly: Clinical Features

- Acral Enlargement and/or Coarse Features: (55–100)
- Sweating: (52–91)
- Menstrual Upset: (32–87)
- Headache: (37–87)
- Arthritis: (30–45)
- Carpal Tunnel: (25–51)
- Diabetes or IGT: (10–68)
- Impaired Potency and/or Libido: (12–46)
- Hypertension: (17–51)
- Visual Field Defect: (4–62)
- Obstructive Sleep Apnea: (7–30)
- Galactorrhea: (5–48)
- Coronary Artery Disease: (11–13)

% with Complication
## Acromegaly: Mode of Presentation

<table>
<thead>
<tr>
<th>Presenting Chief Complaint</th>
<th>Frequency (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual disturbance (females)</td>
<td>13</td>
</tr>
<tr>
<td>Change in appearance/acral growth</td>
<td>11</td>
</tr>
<tr>
<td>Headaches</td>
<td>8</td>
</tr>
<tr>
<td>Paresthesias/carpal tunnel syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus/impaired glucose tolerance</td>
<td>5</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>3</td>
</tr>
<tr>
<td>Decreased libido/impotence (men)</td>
<td>3</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Gigantism</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Chance (detected by physician, dentist, x-ray)</td>
<td>40</td>
</tr>
</tbody>
</table>

*Based on analysis of 310 patients from Klijn et al\(^{57}\) and Nabarro.\(^{82}\)
Acromegaly
Epidemiology

• Incidence: 3-4/million annually
• Prevalence: 40-90 cases/million
• Diagnosis delayed: ~4-10 yrs
• Primary cause: pituitary tumor
  • >75% macroadenomas
• Rare genetic syndromes
• GHRH secreting tumors (Pancreatic, Bronchial)

Macroadenomas 75%
Microadenomas 25%

“Micromegaly”
“Giant” adenomas

Co-secreting Tumors (PRL, TSH)
Double Adenomas
Hereditary Forms of Acromegaly

- Multiple Endocrine Neoplasia, Type 1 (MEN-1)\(^1\)
- Carney Complex (CNC)\(^1\)
- Isolated Familial Somatotropinomas (IFS)\(^2\)
- Familial Isolated Pituitary Adenomas (FIPA)\(^3\)
- McCune-Albright Syndrome

Although these syndromes are very uncommon, information learned from these hereditary syndromes provides insight into the molecular mechanisms underlying the development of sporadic GH-secreting tumors

### Characteristics of 136 pituitary adenomas in MEN-1 patients (France/Belgium Registry)

<table>
<thead>
<tr>
<th>(%) Tumor Types</th>
<th>Macroadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>62% Prolactinomas (n=85)</td>
<td>84%</td>
</tr>
<tr>
<td>9% Somatotropinomas (n=12)</td>
<td>100%</td>
</tr>
<tr>
<td>4% ACTH-secreting (n=6)</td>
<td>50%</td>
</tr>
<tr>
<td>10% Multihormone secreting (n=13)</td>
<td>77%</td>
</tr>
<tr>
<td>15% Non-functioning (n=20)</td>
<td>100%</td>
</tr>
<tr>
<td>LH/FSH-secreting (n=2)</td>
<td></td>
</tr>
</tbody>
</table>

- No genotype-phenotype correlations
- Tumors tend to be larger and more aggressive

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Isolated Familial Somatotropinoma

- 108 patients in 46 families
- Median age at diagnosis: 26 years
- Age at diagnosis <30 years: 73%
  - Males: 57%
- Macroadenoma frequency: 88%
- Gigantism: 12%
- Prolactin immunoreactivity: 57%
  - Most have mild hyperprolactinemia
- Genetic locus (based on tumor deletion mapping and meiotic recombination analysis): 11q13
  - 2.2 Mb interval

“Pituitary Adenoma Predisposition”

Gene: AIP – Aryl Hydrocarbon Receptor Interacting Protein

- Tumor suppressor gene 11q13
- Autosomal Dominant with incomplete penetrance
- Found in the Irish Giant and at least 4 Irish families with Familial Acromegaly
- Estimated to have occurred 1500 years ago
- 3% of sporadic Italian acromegalic patients (Eur J Endocrinol. 2010 Sep;163(3):369-76. Epub 2010)
McCune Albright Syndrome
GNAS1 gene mutation

15 year-old girl
Classical features include:
- fibrous dysplasia of bone (hip, spine, sphenoid)
- “Coast of Maine” hyperpigmentation
- pituitary adenoma, hyperplasia, transitional zones

IGF-1 791 ng/mL (217-589)
GH 26.5 ng/mL

Rx’d SSA

IGF-1 585 ng/mL (217-589)
GH 10 ng/mL
Diagnosis of Acromegaly

IGF-1 Assays

- Usually correlates well with nadir GH on OGTT in acromegaly patients\(^1\)
  - IGF-1 should always be interpreted with reference to GH levels
- Levels are altered with age, gender and pregnancy\(^1\)
- Considered the most sensitive and specific diagnostic test\(^1\)
- However, there are issues with the IGF-1 assay
  - Lack of standardization\(^2\)
  - Difficulty in comparing results between laboratories\(^3\)
  - False negative and false positive IGF-1 levels

Relation of IGF-1 to GH levels
Correlation between total symptoms score and serum IGF-I in patients on medical therapy

R=0.4
P<0.0001

Total symptom score

Serum IGF-I (ng/ml)

Parkinson et al  British Endocrine Society, Belfast 2001
Correlation b/w IGF-I and Clinical Findings

- **Somatomedin-C (Units/ml)**
  - Heel Pad Thickness (mm): $r = 0.73$, $p < 0.00001$
  - Blood Glucose One Hour After Oral Glucose (mg/dl): $r = 0.77$, $p < 0.00001$
  - Fasting Blood Glucose (mg/dl): $r = 0.74$, $p < 0.00001$

Diagnosis of Acromegaly
Use of GH Measurements

- Random GH levels are not generally useful
  - lacks specificity: overlaps with upper range in healthy subjects, and is elevated in patients with poorly controlled diabetes mellitus, renal failure and malnutrition

- Measuring GH during a 75g OGTT is the standard technique for the diagnosis of acromegaly

- False-positives may occur with diabetes mellitus, liver disease, renal disease, adolescence and anorexia nervosa

I tend to employ oGTT in the following scenarios:
- elevated IGF-1 in absence of clinical findings of Acromegaly or pituitary tumor
- post operative patients with high normal IGF-1, possible tumor, GH > 1 ng/mL

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Nadir GH during OGTT by IRMA in Acromegaly

Growth Hormone (ng/ml)

Healthy Subjects
Acromegaly In Remission (Normal IGF-I)
Active Acromegaly (↑ IGF-I)

Freda P et al., J Clin Endocrinol Metab 1998 83;3808
Acromegaly

Goals of Therapy

- “It’s nearly impossible to cure a patient with Acromegaly these days”
- Resect or remove tumor
  - Resolution of mass effects
  - Prevention of progression
- Preserve or improve pituitary function
- Improvement in symptoms and signs
- Improve survival
  - Normalize IGF-1 and GH
Long-term Mortality After Transsphenoidal Surgery

Swearingen, B. et al. J Clin Endocrinol Metab 1998;83:3419
Survival as a function of IGF-1 levels

Holdaway et al. JCEM 89:667-674, 2004
Survival as a function of GH levels

Holdaway et al. JCEM 89:667-674, 2004
SMR in Acromegaly

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized mortality ratio (random) [95% CI]</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swearingen 1998</td>
<td>1.8 [0.4, 4.0]</td>
<td>8.3</td>
</tr>
<tr>
<td>Beauregard 2003</td>
<td>4.8 [2.7, 8.7]</td>
<td>10.0</td>
</tr>
<tr>
<td>Holdaway 2004</td>
<td>3.5 [2.1, 5.8]</td>
<td>10.7</td>
</tr>
<tr>
<td>Kauppinen-Makelin 2005</td>
<td>1.7 [0.9, 3.2]</td>
<td>9.5</td>
</tr>
<tr>
<td>Trepp 2005</td>
<td>1.4 [0.6, 3.3]</td>
<td>8.0</td>
</tr>
<tr>
<td>Final IGF-I elevated</td>
<td>2.5 [1.6, 4.0]</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>( P = 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>Swearingen 1998</td>
<td>0.8 [0.3, 2.1]</td>
<td>7.0</td>
</tr>
<tr>
<td>Beauregard 2003</td>
<td>0.9 [0.3, 2.7]</td>
<td>6.2</td>
</tr>
<tr>
<td>Biermasz 2004</td>
<td>1.2 [0.8, 1.8]</td>
<td>11.6</td>
</tr>
<tr>
<td>Holdaway 2004</td>
<td>1.6 [0.9, 2.9]</td>
<td>10.0</td>
</tr>
<tr>
<td>Kauppinen-Makelin 2005</td>
<td>0.7 [0.4, 1.2]</td>
<td>10.2</td>
</tr>
<tr>
<td>Trepp 2005</td>
<td>1.3 [0.6, 2.8]</td>
<td>8.6</td>
</tr>
<tr>
<td>Final IGF-I normal</td>
<td>1.1 [0.9, 1.4]</td>
<td>53.6</td>
</tr>
<tr>
<td></td>
<td>( P = 0.45 )</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1.6 [1.1, 2.3]</td>
<td>( P = 0.02 )</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 72\%, \ P < 0.001 \)

- Favours decreased mortality in acromegaly
- Favours increased mortality in acromegaly
Criteria for Remission in Acromegaly

• 25 years ago:
  - Random GH < 5 ng/mL
  - GH < 2 ng/mL post oral glucose

• Today:
  - IGF-1 normal
  - Random GH < 1 ng/mL
  - GH < 0.4 ng/mL post oral glucose
### Surgical Remission Rates

<table>
<thead>
<tr>
<th>Pts Range N=98-181</th>
<th>% Cured Micros/Macros</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swearingen</td>
<td>91/48</td>
<td>NL IGF-I and/or GH &lt;2.5 OGTT</td>
</tr>
<tr>
<td>Freda</td>
<td>88/53</td>
<td>NL IGF-I and/or GH &lt;2.0 OGTT</td>
</tr>
<tr>
<td>Beauregard</td>
<td>82/60</td>
<td>NL IGF-I and GH &lt;1.0 OGTT</td>
</tr>
<tr>
<td>Shimon</td>
<td>84/64</td>
<td>NL IGF-I and GH &lt;2.0 OGTT</td>
</tr>
<tr>
<td>Krieger</td>
<td>78/31</td>
<td>Random GH &lt;2.0</td>
</tr>
</tbody>
</table>

The Birmingham pituitary surgery experience

8 surgeons, n=78
1 surgeon, n=66

% post-op GH <2.5 ng/ml

micro: 54 86
macro: 30 52
overall: 33 66

Gittoes et al. QJM 1999;92;741-5
## Post-op Follow-up and Whom To Treat—Current Clinical Practice?

<table>
<thead>
<tr>
<th></th>
<th>Nadir GH &lt;1 µg/L</th>
<th>Nadir GH &gt;1 µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGF-I Normal</strong></td>
<td>No treatment</td>
<td>?</td>
</tr>
<tr>
<td><strong>IGF-I Elevated</strong></td>
<td>“Treat”</td>
<td>Treat</td>
</tr>
</tbody>
</table>
Radiotherapy

- Conventional multi-fractional
- Stereotactic single fraction
  - less radiation to surrounding tissues

- gamma knife
- LINAC
- proton beam
- CPK
Hypopituitarism in 65%
Second neoplasms 60-fold increase
AVM’s
Radiotherapy
A Recommended Approach

• 25 years ago:
  • Conventional XRT in all patients following pituitary surgery

• Today:
  • GKRS when able
  • Age < 45 years
    • Progressive tumor
    • > 1cm residual tumor
    • Biochemically refractory patients

• Age > 45 years
  • Identifiable residual, recurrent, progressive disease
  • Patient preference
Medical Management of Acromegaly

- **Somatostatin Analogs**
  - Bind to Somatostatin receptor
  - Octreotide, Lanreotide, and Pasireotide

- **GH receptor antagonist**
  - Antagonizes GH receptor
  - Pegvisomant

- **Dopamine agonist drugs**
  - Bind to D2 DA receptor
  - Cabergoline and Bromocriptine
Somatostatin Antisecretory Effects

**Somatostatin Antiproliferative Effects**

**Direct**
- Inhibition of autocrine secretion of growth factors and hormones
- Inhibition of growth-factor-induced cell cycle progression
- Possible induction of cell death

**Indirect**
- Inhibition of secretion of growth factors and trophic hormones
- Inhibition of angiogenesis
- Modulation of immune system

---

## Somatostatin Receptor Affinity

<table>
<thead>
<tr>
<th></th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC₅₀ (nM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin-14</td>
<td>1.1</td>
<td>1.3</td>
<td>1.6</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Octreotide</td>
<td>&gt;1000</td>
<td>2.1</td>
<td>35</td>
<td>&gt;1000</td>
<td>5.6</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>&gt;1000</td>
<td>1.8</td>
<td>43</td>
<td>66</td>
<td>0.6</td>
</tr>
</tbody>
</table>

## Receptor Distribution

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH Adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-Acting Somatostatin Analogues – GH and IGF-1 Control

- 38–68% of patients experienced both GH <2.5 ng/mL + IGF-1 normalization\textsuperscript{1,2}
- 54–75% of patients experienced IGF-1 normalization\textsuperscript{1,2}

Long-Acting Somatostatin Analogues — Proven Efficacy in Symptom Control

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of patients with symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18–43%</td>
</tr>
<tr>
<td>Sweating</td>
<td>35–63%</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>26–28%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>46–47%</td>
</tr>
</tbody>
</table>

# Somatostatin Analogs

## Tumor Shrinkage

<table>
<thead>
<tr>
<th></th>
<th>&gt; 50%</th>
<th>20-50%</th>
<th>% with any shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide LAR</td>
<td>0</td>
<td>35</td>
<td>43 (22/51)</td>
</tr>
<tr>
<td>Lanreotide SR</td>
<td>1</td>
<td>11</td>
<td>17 (33/194)</td>
</tr>
<tr>
<td>Primary therapy</td>
<td>7</td>
<td>32</td>
<td>48 (122/256)</td>
</tr>
</tbody>
</table>

Freda PU. *J Clin Endocrinol Metab.* 2002;87:3013-3018.
Pre and post treatment MRI studies
Pre and post treatment MRI studies
### Most Common Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Number and percentage of patients</th>
<th>Studies 1 &amp; 2 (N=170)</th>
<th>Overall pooled data (N=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Patients with any adverse reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>92</td>
<td>356</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>48</td>
<td>155</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>Flatulence</td>
<td>12</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Loose stools</td>
<td>16</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>45</td>
<td>27</td>
<td>85</td>
</tr>
</tbody>
</table>

GH Action action and Pegvisomant

[Diagram of GH signaling pathways]

[Diagram of amino acid sequence of Pegvisomant protein]
Percentage of Patients Achieving a Normal Age-Related Serum IGF-I with Pegvisomant

- Placebo: 7%
- 10 mg: 54%
- 15 mg: 81%
- 20 mg: 89%

* P < 0.0001 v. placebo

with doses up to 40 mg IGF-1 normal in 97%

Trainer et al NEJM 2000:342;1171-1177
IGF-I at baseline and after 12 months pegvisomant

van der Lely et al Lancet 2001:358;1754
Change in Ring Size following Pegvisomant Treatment

Trainer et al NEJM 2000;342;1171-1177
AcroStudy

Pegvisomant in routine clinical use

- 1288 treated patients
- Mean of 3.7 years
- Pituitary tumor increases in size in 3.2% of patients
- Abnormal LFT’s in 2.5%
- Injection site reactions in 2.2% of patients
- 63% of patients after 5 years with a normal IGF-1 on mean dose of 18 mg.

Van der Lely et al. J Clin Endocrinol Metab Feb 22, 2012
Acromegaly
Efficacy of DA Agonist drugs

• Bromocriptine
  • High doses (30 mg/d) oft required
  • 15% of aptients normalize IGF-1

• Cabergoline
  • 3-5 mg/week in divided doses
  • 20-40% normalize IGF-1
  • Greater likelihood of response in patients with mixed tumors that co-secrete PRL

I often utilize these agents in elderly patients and find a surprisingly high response rate in elderly women.
Serum IGF-I in patients with acromegaly on cabergoline (max. dose 3.5 mg/week)
Case 3
IGF-I data

![Chart showing IGF-I data with annotations for Sandostatin LAR, Somavert, and Cabergoline start and stop dates.]

- **TSATSA & CPK**
- **Start-Sandostatin LAR-Stop**
- **Start-Somavert-Stop**
- **Cabergoline**
Management of Acromegaly

- Individualize therapy
  - Algorithms don’t work very well
  - Patient preference
  - Specific needs
- Dovetail strategic use of surgery and radiotherapy as well as specific medical therapy
- Growth and change is inevitable!