Acromegaly

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Academic Half Day
Friday, Feb 12, 2016

Disclosures

- None!

Objectives

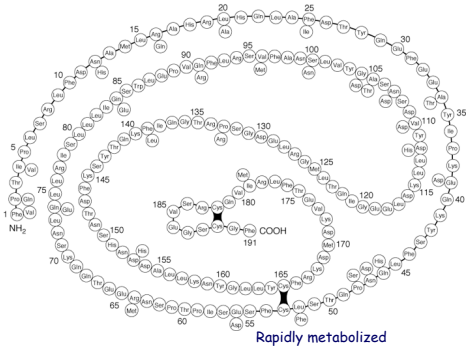
By the end of this presentation, you should know:

1. The differential diagnosis of acromegaly
2. The challenges in making the diagnosis of acromegaly
3. The principles of therapy including when to use:
   a. Drugs (octreotide LAR, cabergoline, pegvisomant),
   b. Surgery
   c. Radiation

Overview

- Background/Pathophysiology
- How to diagnose acromegaly
- Treatment options
- Monitoring for complications

Human Growth Hormone



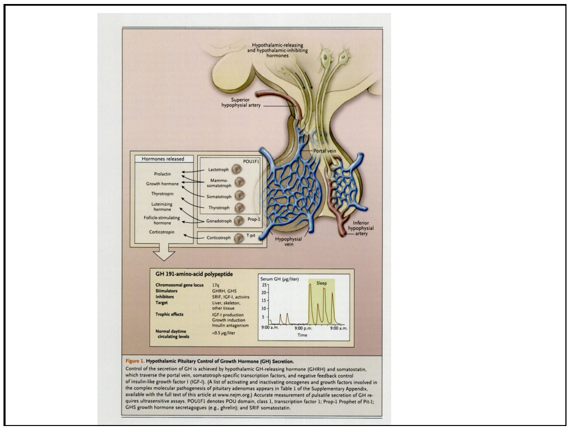
Rapidly metabolized

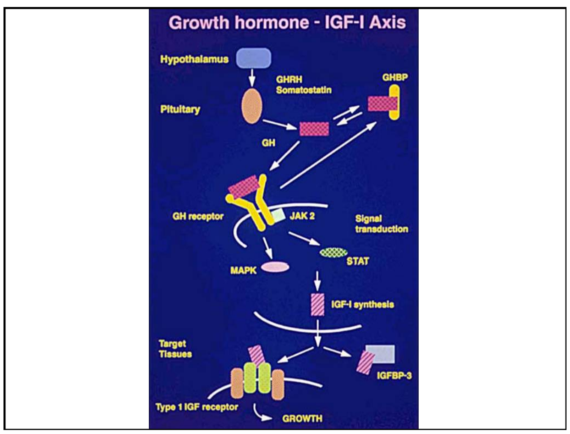
T1/2 6-20min

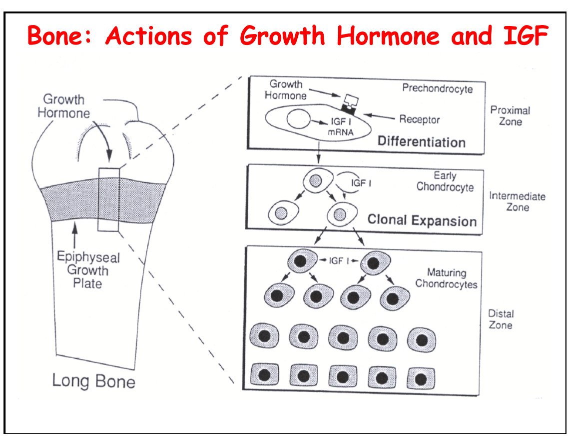
Ganong

Actions of GH and IGF-1

- GH
  - Increased hepatic glucose output→ increased glucose
  - Na+ retention
  - Decreased insulin sensitivity
  - Lipolysis
  - Protein synthesis
  - Epiphysial growth
  - IGF-1 production
- IGF-1
  - Insulin-like action
  - Antilipolysis
  - Protein synthesis
  - Epiphysial growth




Growth hormone - IGF-I Axis
Hypothalamus
GHRH
Somatostatin
GHBP
Pituitary
GH
GH receptor
JAK 2
Signal
transduction
STAT
MAPK
IGF-I synthesis
Target
Tissues
IGFBP-3
Type 1 IGF receptor
GROWTH


Bone: Actions of Growth Hormone and IGF
Growth
Hormone
Epiphyseal
Growth
Plate
Long Bone
Growth
Hormone
Prechondrocyte
IGF I
mRNA
Receptor
Differentiation
Proximal
Zone
IGF I
Early
Chondrocyte
Clonal Expansion
Intermediate
Zone
IGF I
Maturing
Chondrocytes
Distal
Zone

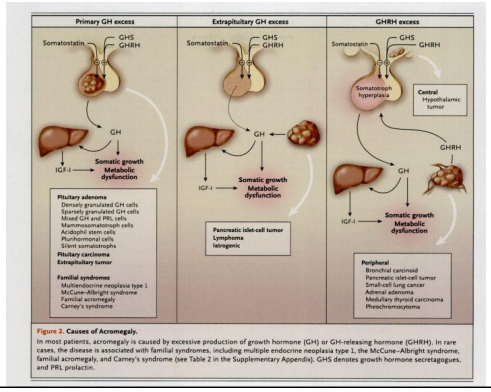


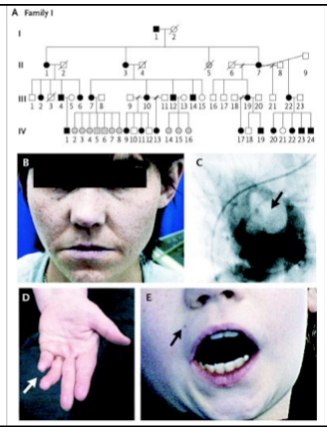
Figure 2. **Causes of Acromegaly.**

In most patients, acromegaly is caused by excessive production of growth hormone (GH) or GH-releasing hormone (GHRH). In rare cases, the disease is associated with familial syndromes, including multiple endocrine neoplasia type 1, the McCune–Albright syndrome, familial acromegaly, and Carney's syndrome (see Table 2 in the Supplementary Appendix). GHS denotes growth hormone secretagogues, and PRL prolactin.

Genetic causes of acromegaly…

What's the diagnosis?

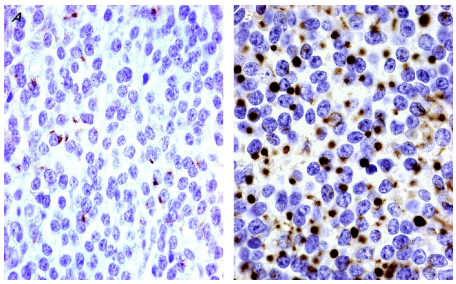
- 1. Primary pigmented nodular adrenocortical disease (ACTH- independent Cushing's)
- 2. Lentiginosis (including blue nevi)
- 3. Other tumors:
  - Myxomas
  - Schwannomas
  - Acromegaly: adenoma or mammosomatotroph hyperplasia
  - Testicular Sertoli cell tumor
  - Thyroid tumors, etc



FIPA: Familial Isolated Pituitary Adenoma:
mutation in AIP *aryl hydrocarbon–interacting protein* gene

The skeleton of Charles Byrne, Professor Márta Korbonits and patient Brendan Holland. (

Densely and sparsely granulated adenomas



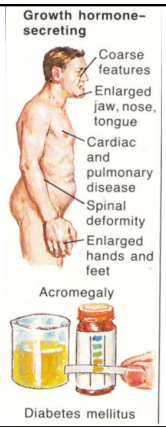
Sparsely granulated vs densely granulated predicts response to octreotide

Bhayana JCEM 2005

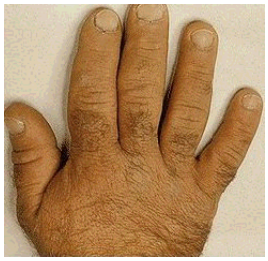
- Univariate analysis for responders
  - densely granulated somatotroph adenomas (80% vs. 43.8%; P = 0.024
  - to be older (51.3 vs. 38.2 yr)
  - to have smaller tumors
  - to require a lower maximum dose of SSA (24 vs. 31 mg every 4 wk; P = 0.013).
  - to have lower
    - baseline IGF-I (453 vs. 716 microg/liter; P < 0.001)
    - GH levels (2.7 vs. 7.8 microg/liter; P < 0.05)
- Multivariate analysis
  - densely granulated adenoma the strongest predictor of complete response

Symptoms in acromegaly

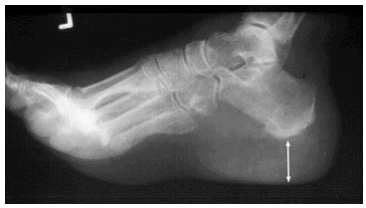
- Headache, hyperhydrosis, fatigue
- Changes in face/dentition/hands/feet
- Visual field defect
- Carpal tunnel syndrome
- Metabolic: hyperglycemia, dyslipidemia, hypertension
- Cardiovascular disease
- Hypertrophic arthritis (osteoarthritis)
- Sleep apnea
- Colon polyps
- Hypogonadism
- Kidney stones
- Benign prostatic hypertrophy
- Multinodular goiter



Typical hands



Increased heel pad thinkness



Diagnosing acromegaly

- Clinical picture
- IGF-1 above the ULN (corrected for gender and age)
- Non-suppressible GH
  - 75 g oral glucose challenge, 2 hour:

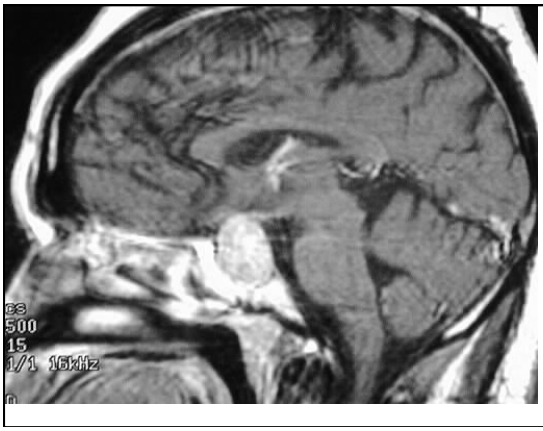
Time	0	30'	60'	90'	180'
Glucose	9.8	15	20	21	18
GH	5	5	7	5	4

What causes misleading IGF-1 levels?

Falsely lowered IGF-1	Falsely raised IGF-1
Malnourished state	Pregnancy
Liver disease	Puberty/Adolescence
Hypothyroidism	Uncontrolled thyrotoxicosis
Poorly controlled diabetes	Glucocorticoid Rx
Obesity	
Oral contraceptives	

What causes misleading GH levels?

High/nonsuppressed GH and low IGF1	High GH and normal/high IGF-1
Fasting and anorexia	Pregnancy
Poorly controlled diabetes	Puberty
Renal disease	Uncontrolled hyperthyroidism
Liver disease	
Estrogen Rx/Pregnancy	



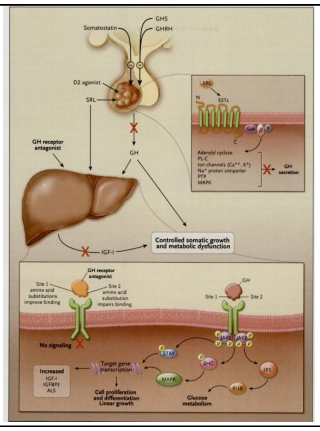
What would you do now?

What treatment would you offer?

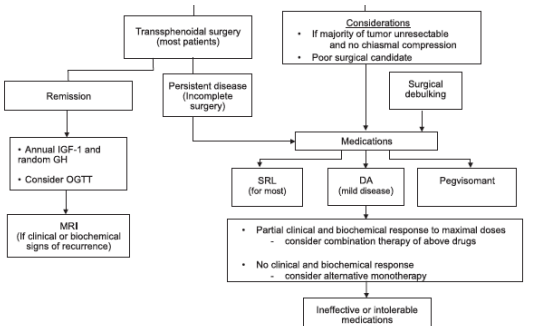
- Would you recommend surgery? Would you pre-medicate the patient?
- If the patient goes to surgery, how will you assess him postoperatively?
- If they require medical therapy, what are your options and how would you decide which medication to use?
- When would you recommend radiation? Which type of radiation would you recommend?

What are our options for treatment?

- Medical
  - Octreotide
  - Cabergoline
  - Pegvisomant
- Surgical
- Radiation
  - Gamma knife
  - Fractionated



Treatment of acromegaly ES Guidelines 2014



Adapted from Figure 1, Katznelson et al, JCEM 2014;99:3933-3951.

What are our treatment goals?

1. Normalize both IGF-1 and suppressed GH.
   – Increased cardiovascular risk with elevated GH levels
   – Patients feel unwell with suboptimal GH levels
2. Ensure no mass effect/tumor growth
3. Manage the complications

Mortality in acromegaly: a meta-analysis

Dekkers JCEM 2008

- Meta-analysis of 16 trials
- Primary endpoint: weighted average of the standardized mortality ratio (SMR)
- Results:
  - Overall: SMR 1.72 (1.62-1.83)
  - Post surgery: SMR 1.32

Impact of treatment

- Longer survival is predicted if:
  - GH < 2.5 ug/L
  - Younger age
  - Shorter duration of disease
  - No hypertension
    - Holdaway Pituitary 1999
    - Kauppinen-Makelin JCEM 2005

How do you prescribe the drugs?

Octreotide

- Indications:
  - After failure of surgery
  - First line if surgery contraindicated
  - ? First line if surgery won't be curative
- Effectiveness:
  - ↓ IGF-1 50-70%
  - ↓ tumor size 30-50% of patients
  - Improvement in LVH, BPH, sleep apnea
- Side effects:
  - GI cramps, diarrhea (usu temporary)
  - Gallstone "sludge"
  - Hyperglycemia
- Dose:
  - Try sc first to assess for side effects
  - Octreotide LAR 20 mg q monthly
  - increase dose q 2- 3 months prn→30mg → (40 mg) monthly
- Cost: for 20 mg: $25,000/yr

Cabergoline

- Indications:
  - Co-prolactin secreting tumors
  - Pts with mild-moderate increased IGF-1 (25-50% above ULN)
  - In combination with SSA if partial response to SSA
- Effectiveness:
  - ↓ IGF-1 < 300 in 35% of patients
- Side effects:
  - Nausea, dizziness
- Dose:
  - Cabergoline 1-2 mg weekly in divided doses
    - Abs R JCEM 1998
- Cost: 2 mg/wk = $5000/year

Pegvisomant

- Indications:
  - Failure of surgery and other medical options
- Effectiveness:
  - Reduce-normalize IGF-1 levels in > 90% pts
  - Tumor may grow!
- Side-effects:
  - 20% of pts get increased AST
    Check q month x 6, then q 6 months, d/c if >3 fold up
- Dose: 10-30 mg sc daily
  - Load with 40 mg, then 10 mg daily, check IGF-1 q 4-6 weeks, increase by 5 mg increments prn
- Cost: for 20 mg is $80,000/yr

Transphenoidal surgery

- Mass effect: esp visual compromise
- Assess for cure and for hypopituitarism post-op
- Microadenomas and noninvasive macroadenomas:
  - 60-80% cure rate

Radiation

	Conventional fractionated radiation	Gamma knife
Time to remission	5 yrs 10-20 yrs for full effect	1-1.5 yr
Hypopituitarism	50%	28%
Loss of vision		Must be > 3 mm away from optic chiasm
Radiation necrosis	Yes	Yes
Second malignancy	Yes	Yes

- What are the long-term management issues, besides hormonal hyper-secretion and mass effects, and how would you monitor for them?

Monitoring for complications of acromegaly

Disease-related	**Headache, fatigue, hyperhydrosis IGF-1 q 6 mo, suppressed GH q yr**
Metabolic	DM, lipids, BP, Ca2+, BMD
CVD	LVH, CAD, 2D ECHO;
Skeletal	Arthritis, CTS, OP, jaw malocclusion
Respiratory	Sleep apnea
GI	Colon polyps
GU	Kidney stones, BPH
Other	Hypopituitarism, MNG
Mass effect	Visual field defect, MRI

- What is different about the etiology of GH excess in the patient with gigantism compared to the patient with acromegaly?
- How does your investigation and treatment different than in the adult?

What is different about the etiology of GH excess in the patient with gigantism vs acromegaly?

- Very rare: 0.6% of pituitary adenomas
- More often due to hypothalamic GHRH excess
- Mammosomatotroph most commonly affected
- Genetic syndromes:
  - McCune-Albright: 20% have increased GH, can be normal height with premature puberty
  - MEN1: usually 4th and fifth decades, 1 pt 5 yo
  - Carney's complex
  - NF-1 + optic nerve fibromas
  - Acromegaly kindreds: AD, as young as 9 yo

How is the presentation different than in the adult?

- Can get obesity and macrocephaly at presentation
- Can get ketoacidosis in adolecents
- Differential for tall stature
  - Genetic tall stature
  - Delayed puberty
  - Hyperthyroidism
  - Syndromic or chromosomal cause of tall stature (eg, XYY syndrome).

How does your investigation and treatment different than in the adult?

- Glucose suppression of GH:
  - In one prospective study of 126 tall adolescents (height 3.1 +/- 0.8 SDS), 31 percent of normal subjects failed to suppress GH
- IGF-1 levels
- MRI
- Treatment the same: Med vs surgery, avoid radiation

Conclusions

1. Think of the diagnosis, and other conditions that can alter lab results

2. Aim for normalization of IGF-1 and suppressed GH
   Will often require multiple modalities

3. Monitor for complications