Growth Disorders...
Too Tall Too Small

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Introduction

Dwarfism, gigantism, and acromegaly are three rare but devastating growth disorders.

This presentation will outline the main etiologies, manifestations, diagnostic modalities, and treatment options for these three conditions.

Interlaced within the discussion are short bios of historical figures afflicted with one of these growth aberrancies.
Normal Growth

- Results from the absence of chronic disease
  - Proper interaction of:
    - Genetic
    - Nutritional
    - Metabolic
    - Endocrine factors
GROWTH EVALUATION

SHORT
- Normal Variant
- Genetic Short Stature
- Constitutional Delay

ABNORMAL
- Chromosomal/syndromes
- Disproportional

PROPORTIONAL
- PRENATAL-ONSET Embryonic
- Post-Natal Onset Childhood Puberty

Limit to primary GH disorders
How Tall Will My Child Grow?
Height calculations for your child.

- Add the mother's height and the father's height in either inches.
- Add 5 inches for boys or subtract 5 inches for girls.
- Divide by two.
- Another way to estimate a child's adult height is to double a boy's height at age 2 or a girl's height at age 18 months.
Overview of anterior pituitary hormone functions

- Prolactin
  - Breast
  - Milk
- Growth hormone
  - Liver
  - IGF-1
- TSH
  - Thyroid gland
  - T3 & T4
- ACTH
  - Adrenal cortex
  - Many tissues
- Gonadotropins (LH/FSH)
  - Gonads
- Sex steroids
  - Gamete production
- Sex characteristics
  - Reproduction

Intermediary metabolism

Breast, liver, cortisol, T3 & T4, many tissues, sex steroids, sex characteristics, reproductive system.
**History of Growth Disorders**

- 1921 – Growth promoting factor in the pituitary was first discovered
- 1944 – Bovine GH isolated
- 1960s – Children 1st Rx with cadaveric hGH
- 1985 – rhGH therapy becomes available
# 1. An adult patient is measured at a height of 4 feet tall. The appropriate term for this patient is which of the following?

A. Midget
B. Small-fry
C. Little person or little people
D. Munchkin
E. Muggle
Short Statue

- Little People of America (LPA)
- Define: Dwarfism
  - Medical or genetic condition
  - Adult height ≤ 4’10”
  - Disproportional
    - Achondroplasia – autosomal dominant – 1:15000-30,000
      - The FGFR3 gene mutation: provides instructions for making a protein called fibroblast growth factor receptor 3.
    - Spondyloepiphyseal dyplasia – 1:95,000
    - Diastropic dyplasia – 1:110,000
    - Osteogenesis imperfecta (bone fractures and blue sclera)
  - Proportional
    - Growth hormone deficiency (absolute or functional)
Dwarfism – acceptable term

What is a midget?
- Unacceptable term
- Term dating to times of “freak shows”

Little People – acceptable term
- LPAonline.org

The “Foos” family

Achondroplasia
Peter Dinklage was born in Morristown, NJ in 1969 of two normal-sized parents. Which of the following characters has he portrayed?

- 1. Tyrion Lannister
- 2. Theon Grayjoy
- 3. Jorah Mormont
- 4. Samwell Tary
- 5. Stannis Baratheon

All people with achondroplasia have short stature. The average height of an adult male with achondroplasia is 131 centimeters (4 feet, 4 inches), and the average height for adult females is 124 centimeters (4 feet, 1 inch). Characteristic features of achondroplasia include an average-size trunk, short arms and legs with particularly short upper arms and thighs, limited range of motion at the elbows, and an enlarged head (macrocephaly) with a prominent forehead. Fingers are typically short and the ring finger and middle finger may diverge, giving the hand a three-pronged (trident) appearance. People with achondroplasia are generally of normal intelligence.
Polypeptide hormones must be given by injection

199 amino acid polypeptide

70 amino acid polypeptide

Growth hormone

liver

IGF-1

Bone

Soft tissues

Growth

Many tissues

Intermediary metabolism

http://www.umanitoba.ca/dnalab/med/pit2.gif

www.ghresearchsociety.org/
# 2. Which of the following statements regarding Tom Thumb is **NOT** true?

A. He was born in Bridgeport, Connecticut
B. He married a “normal” height woman
C. He had a low IGF-1 concentration
D. He had a low growth hormone concentration
E. He worked in the circus
General Tom Thumb
(1838-1883)

Born Charles Sherwood Stratton
Stood 3 feet, 4 inches tall
Discovered by P.T. Barnum
Toured the world
Performed for many world leaders, including Abraham Lincoln, Queen Victoria of England, and Queen Isabella of Spain
Became very wealthy through his years in show business

Drimmer, *Very Special People*, 1973

http://bullseyedesigns.com/sideshow
Dwarfism

Causes of Growth Hormone Deficiency

- Congenital (5-30% familial)
  - Several genetic mutations affecting gene transcription or affecting the GH molecule

- Pituitary/midline developmental anomalies

- Postnatally: acquired causes
  - Tumors
  - Trauma
  - Radiation
  - Granulomatous
  - Infiltrative
  - Infectious
  - Autoimmune
  - Idiopathic
Dwarfism
Growth Hormone Deficiency

Manifestations:
- Growth retardation – proportionate dwarfism
- Hypoglycemia
- Micropenis
- Craniofacial abnormalities
- “Chubby”
- Retarded bone age
- Delayed puberty

Tom Thumb married Livinia Warren in Feb 63. She was 32” tall. Weight=29 pounds
Dwarfism: Growth Hormone Deficiency

Importance of Growth Charts Objective Data

Evaluation

- Accurate height
- Height/weight/proportions
- Height velocity
- Screening labs
  - CBC, ESR
  - Tissue trans-glutaminase
  - Chem Profiles
  - UA, urine Culture
  - Bone age
  - TFT (T4 + TSH)
  - IGF1

Additional labs/tests:
- IGFBP-3

Karyotype: Down’s, Turner’s
Dwarfism: Growth Hormone Deficiency

Diagnosis

- Low IGF-1 and low IGFBP-3
  - Integrated concentration of secreted GH
- Assess stimulated GH response (2 tests)
  - Arginine
  - Clonidine
  - Glucagon
  - Insulin tolerance test
- Image the pituitary
Dwarfism
Growth Hormone Deficiency

- Treatment: Growth Hormone (Somatropin)
  - Recombinant DNA technology
  - Subcutaneous injection
  - Several commercial brands available
  - Indications:
    - GH deficiency in children
    - GH deficiency in adults
    - Turner’s syndrome
    - Prader-Willi syndrome
    - Idiopathic short stature
  - Cost: $200 per week (based on 40 pound child)
# 3. Which of the following statements is true regarding Laron Syndrome?

A. People with the disorder have low GH levels
B. People with the disorder have GH receptor defects
C. People with the disorder have disproportionate growth
D. People with this disorder paradoxically have elevated IGF-1 concentrations
E. Many people in the villages of Honduras have this syndrome.
Dwarfism
Growth Hormone Resistance

Laron Syndrome: Growth hormone receptor defect

- Due to growth hormone receptor mutation
- Approximately 30 mutations have been isolated
- Mountains of Ecuador 1/3 world’s population of Laron Syndrome
- No diabetes, no cancer

Localization to receptor is supported:
- Clinical improvement with IGF-I administration
- No effect from GH administration

Resistance can be partial, with variance in clinical presentation

Hull, 1999
Dwarfism
Growth Hormone Resistance

Increased GH but decreased IGF-I

- Growth retardation
- Acromicria
- Micro-orchidism and pubertal delay
- Obesity
- Neurologic underdevelopment
- Laryngeal narrowing
- Disproportionately long torso
- Cholesterol abnormalities
- Osteoporosis
- Small heart

10 year old Laron Dwarf
Normal Intelligence

Laron, 1999
Dwarfism
Growth Hormone Resistance

Treatment: Injectable IGF-1

Decreases
- Adiposity
- Cholesterol
- Glucose intolerance
- Morbidity

Increases
- Linear velocity
- Head circumference
- Sexual development
- Renal function

Laron, 1999
Lucia Zarate
(1864-1890)

At birth, weighed 8 oz; length of 7 inches
As an adult, weighed less than five pounds; height of < 20 inches

World’s Shortest Woman

In United States, made $20/hr !!

http://bullseyedesigns.com/sideshow
Dwarfism
Summary

Important to identify dwarfism early

Define etiology: GH deficiency
GH resistance

Effective treatments available which promote growth and decrease morbidity
Goliath
The Philistine Giant

Height of six cubits and a span
Translates to roughly three meters, or over nine feet
Armor weighed 125 lbs
The iron point of his spear weighed 15 lbs

Story of David and Goliath
I Samuel 17:4-7, Holy Bible, NIV

www.orura.com/cards/p35.jpg
Gigantism and Acromegaly

Gigantism denotes an environment of excessive growth hormone prior to closure of epiphyseal growth plates (before puberty)

Proportionate growth
Probable etiology in patients >7’4”

Acromegaly excessive growth hormone after closure of epiphyseal growth plates

Disproportionate growth

Eugster, 1999
Sotos, 1996
Gigantism and Acromegaly

Incidence
3rd decade
3/million/yr

Prior to closure of plates
About 100 cases documented

10% are Giants

Eugster, 1999
Maugans, 1995
Sotos, 1996

Typical physician sees only a few in his/her career
Andre the Giant
(1946-1993)

Born Andre Rousimoff in Grenoble, France

1988 – briefly the WWF champion
1989 – WWF tag team champion with Haku
(as part of the Colossal Connection)

Final height of 7’4”
Top weight of 520 lbs

http://www.puroresu.com/wrestlers/andre/

members.tripod.co.uk/Bryvoski/ Bryvoski-net/Gallery/andre.jp
Andre the Giant

Fezzik in The Princess Bride (1987)


http://www.puroresu.com/wrestlers/andre/
# 4. Which of the following is the most common source of ectopic GHRH associated with acromegaly or gigantism?

A. Pheochromocytoma
B. Germ cell tumors
C. Pancreatic islet cell tumors
D. Carcinoid
E. Teratomas
Gigantism and Acromegaly

Hypersecretion of Growth Hormone

Pituitary Source (Primary)
- Pituitary adenoma (98%)

Extra-pituitary Source
- Hypothalamic GHRH hypersecretion with resulting pituitary hyperplasia
- Intracranial GHRH secreting tumor
- Ectopic sources GHRH (e.g., carcinoid)
- Ectopic GH secretion: pancreatic lesions

Eugster, 1999
Gigantism and Acromegaly

Pituitary Adenomas

Somatotrophs (GH)
- Chromophobes > Eosinophilic tumors
  - Larger
  - More aggressive
  - Most common

Mammosomatotrophs
- Monomorphous
- (25%)

Mixed Mammotroph-Somatotroph
- Bimorphous
- PRL
- GH

Plurihormonal
- GH/thyrotropin, or GH/prolactin/alpha subunit
- (10%)

Others
- MAS, MEN-1

Acidophilic Stem Cell
- PRL > GH

Sotos, 1996
Gigantism and Acromegaly

GHRH Tumors

Extracranial
- Carcinoid 69%
- Bronchial Adenomas
- Pheochromocytoma
- Paraganglioma

Intracranial
- Islet Cell Tumor 23%
  - Adrenal Adenoma
- Gangliocytomas
- Hamartomas
- Ganglioneuromas

Sotos, 1996
Chang Woo Gow (1841-1893)

The Chinese Giant

Final height of nearly eight feet (recorded at 7’8 ½ ”)

Reported that he had a taller sister!

Spoke six languages

Art collector

Displayed his collection at his home

http://www.ashleighhotel.co.uk/chang.html
Chang Woo Gow (1841-1893)
The Chinese Giant

http://www.ashleighhotel.co.uk/chang.html
Gigantism and Acromegaly
Clinical Manifestations

George Auger
1883-1922

Most common:
- Growth of soft tissue
- Thickening of bones
- Acral growth
- Sinus enlargement
- Cardiomegaly
- Increases in height
- Cholelithiasis
- Headache

The Welsh Giant

Maugens, 1995
Sotos, 1996

George Auger was a Welsh giant who lived from 1883 to 1922. He was known for his impressive height and was often featured in sideshows. His most common clinical manifestations included growth of soft tissue, thickening of bones, acral growth, sinus enlargement, cardiomegaly, increases in height, cholelithiasis, and headache. The image shows a photograph of George Auger and his family.
# Gigantism and Acromegaly

## Clinical Manifestations

<table>
<thead>
<tr>
<th></th>
<th>Gigantism</th>
<th>Acromegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Acceleration</td>
<td>100%</td>
<td>14-19%</td>
</tr>
<tr>
<td>Acral Growth</td>
<td>40-100%</td>
<td>100%</td>
</tr>
<tr>
<td>Soft-tissue Enlargement</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bone Thickening</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
<td>75-87%</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

Adapted from Sotos, 1996, Table 2. Pg 583
Gigantism and Acromegaly

Clinical Manifestations

- Diabetes/glucose intolerance
- Hypertension (HTN)
- Heart failure (CHF)
- Visual Changes
- Diabetes insipidus (DI)
- Polydipsia
- Weight Gain
- Osteoporosis
- Sellar Enlargement
- Paresthesias
- Hyperpigmentation
- Arthralgias
- OSA
- Sixth Nerve Palsy
- Carpal Tunnel Syndrome
- Cholelithiasis
- Thyroid Goiter/Nodules
- Weakness
- Enlarged Organs
- Cholelithiasis
- Alterations in Libido
- Increased Metabolism
- Increased Perspiration
- Skin tags

Maugins, 1995
Sotos, 1996
Acromegaly
Gigantism and Acromegaly

Malignancy


http://www.coloncancer.org/KF_01.jpg

www.enteract.com/~rosa/prostatedrawing.html
Gigantism and Acromegaly

Malignancy

Conclusive evidence of correlation between acromegaly and increased colon cancer risk (RR of 13.4)

Colonic polyps
- Right-sided predominance
- Increased prevalence, size
- Multiplicity
- Increased dysplasia
- Increased transformation

IGF-I can trigger transcription of c-myc

Screen acromegalic patients as high-risk
- First colonoscopy at age 40
- If polyps found, polypectomy and increased surveillance

Jenkins, 2001

http://www.coloncancer.org/KF_01.jpg
Gheorghe Muresan
Tallest NBA Player

7 foot 7 inches tall
Born in Romania, 1971
Started playing basketball at age 14
On Romanian National Team by age 16
To NBA in 1994, played 6 years
Professional highlight was starring in “My Giant” with Billy Crystal

movieweb.com/movie/mygiant
www.guinnessworldrecords.com
Gheorghe Muresan
Tallest NBA Player

With Billy Crystal

My Giant

movieweb.com/movie/mygiant
5. The most appropriate screening test for a patient with suspected acromegaly is which of the following?

A. Measurement of IGF-1 concentrations
B. Oral glucose tolerance test with measurement of IGF-1 concentrations
C. Measurement of an early morning GH concentration
D. Measurement of a late night salivary GH concentration
E. MRI sella
Gigantism and Acromegaly

Diagnosis

Growth Hormone
IGF-1

GH is pulsatile (random level inadequate, though GH is < 1ng/ml for half of the day in normal adult individuals)
IGF-I (somatomedin C) is non-pulsatil
- Must be compared with age/gender
- Preferred over GH
- High IGF-I is very specific for acromegaly (unless pubescent or pregnant)

- IGF-1 is the screening test for acromegaly

Maugens, 1995
Melmed, 1998
Gigantism and Acromegaly
Diagnosis

History and Physical Suggestive

Screen with IGF-I

Normal

Abnormal

Glucose Tolerance Test With GH Suppression

Gold Standard Diagnostic Test

No acromegaly

Abnormal

Pituitary MRI

Normal (ectopic)

?Other Radiologic Tests
Measure GHRH
(Chest x-ray, mammogram, CT/MRI of Abd/Chest/Hypothalamus)

< 1cm
Surgery
And/Or
Medical Tx
or Radiotherapy

> 1cm
Surgery
then
Medical Tx or Radiotherapy
Gigantism and Acromegaly

Diagnosis

Gold Standard Diagnostic Test

Glucose Tolerance Test With GH Suppression

- 75g of glucose after overnight fast
- Baseline glucose and GH
- Repeat levels at 30, 60, 90, and 180 min
- Look for suppression of GH to < 1ng/ml
- If no suppression, acromegaly

Guistina, 2000
Maugens, 1995
Gigantism and Acromegaly

Diagnosis

Pituitary MRI

(bufaloneuro.com/pittumo/ ENDOPI.HTM)
Sandy Allen [1955-2008]
Former Tallest Woman

Height of 7’ 7 ¼”
Pituitary surgery in 1977
Lived in Indianapolis, IN

www.globalmark.com/sandy/diff02.jpg

www.amazon.com

www.guinnessworldrecords.com
De-Fen Yao

Tallest living woman
Reported height of 7’ 8 ½”
Lives in China
Now recognized by
Guinness Book of World Records

http://www.tallwomen.org/tallest/
Gigantism and Acromegaly

Treatment

**Goals of Therapy**

Elimination of mass effect of tumor
Normalization of GH and IGF-1 levels
  GH<1 and normal IGF-1 for age/sex
Improve morbidity and mortality
  - No control…3.5X mortality
  - Appropriate control…normal mortality

Guistina, 2000
When surgical intervention fails to cure acromegaly, which of the following **WOULD NOT** be an appropriate adjuvant treatment?

A. Gamma knife surgery
B. Sandostatin LAR
C. Lanreotidte
D. Teraparatide
E. Repeat surgical intervention
Gigantism and Acromegaly

Treatment

Five Main Treatment Options

- Surgery
- Somatostatin Analogs
- Radiotherapy
- Dopamine Agonists
- Growth Hormone Receptor Blockers

Melmed, 1998
Gigantism and Acromegaly

Treatment

Surgery
Preferred option if possible
70-90 % cure of disease in patients with microadenomas
20-50 % cure of disease in patients with macroadenomas
GH decrease is rapid post-op
IGF-1 decrease is delayed
> 40% of all surgical cases, however, result in inadequate control (GH> 5ng/ml)

Giustina, 2000
Melmed, 1998

Gigantism and Acromegaly

Treatment

Somatostatin Analogs: octreotide and lanreotide

Longer lasting than somatostatin
Octreotide half-life is 2 hours
Requires TID dosing subcutaneous injection
Effective

95% of acromegalic patients see reduction of GH secretion
60% of patients see normalization of IGF-I

Melmed, 1998
Gigantism and Acromegaly

Treatment

Adverse Reactions to Octreotide

Cholesterol gallstones (25%)
Bradycardia (25%)
GI distress

Usually Subclinical
Usually NOT Subclinical

Melmed, 1998
Gigantism and Acromegaly

Treatment

**octreotide**

Slow Release Formulation Given I.M.
Sustainable levels for a four week period
Control in 70% of patients (who are sensitive to octreotide)
Shrinks tumor mass

or

**Somatuline Depot**

**Lanreotide**

Giustina, 2000

http://www.acromegalyinfo.com/prof_home/prof_home.html
Anna Swan and Martin Bates
“The Nova Scotia Giantess and the Kentucky Giant”

Swan + Bates = Married

7 feet 5.5 inches + 7 feet 2.5 inches = 14 feet 8 inches

2 babies, both died near birth:
Giant Baby…
23 ¾ lbs, 30 inches long

http://bullseyedesigns.com/sideshow
Martin Bates

Ohio Historical Marker

"The Giants of Seville"

Seville's most famous residents, Captain Martin Van Buuren Bates (1845-1910) and Anna Swan Bates (1848-1889) settled here in 1873. Their notoriety stemmed from their dramatic stature: Martin, a former Confederate soldier from Kentucky, stood 7 feet 6 inches tall; Anna, a schoolteacher from Nova Scotia, stood 7 feet 11½ inches tall. They met on the carnival circuit in New Jersey in 1871 and wedded in England the same year in a ceremony orchestrated by Queen Victoria.

The Ohio Bicentennial Commission
The Longaberger Company
Seville Kiwanis and Lions Clubs
The Village of Seville
The Seville Historical Society
The Ohio Historical Society 2000
Gigantism and Acromegaly

Treatment

Growth Hormone Receptor Blocker

- Pegvisomant (Somavert®)
- Subcutaneous injection daily
- Effectively reduces IGF-1
- No effect on tumor mass
- Similar cost of Sandostatin LAR
- Can be added to Sandostatin tx or lanreotide
Gigantism and Acromegaly

Treatment

Growth Hormone Receptor Blocker
Gigantism and Acromegaly

**Treatment**

**Dopamine Agonists**

- Pergolide, bromocriptine, cabergoline

Inhibit secretion of GH in those with mammosomatotrophic tumor

Poor efficacy

- IGF-I levels normalize in only 10% of patients

Many side effects

Melmed, 1998
Gigantism and Acromegaly

Treatment

Radiotherapy

Delayed benefit (years)
Only 50% controlled at 10 yr mark
Potential for HP axis dysfunction
Preliminary results of trials involving stereotactic radiosurgery are promising

Melmed, 1998
Giustina, 2000
Gigantism and Acromegaly

Treatment Follow-up

Labs at 6-12 weeks S/P treatment
GH : < 1 ng/ml
IGF-I : normalized
Assess other pituitary function

MRI
Visual Field exam

Giustina, 2000
Gigantism and Acromegaly

Treatment Follow-up

- Lifelong surveillance
  - Recurrence
  - Colonic polyps/cancer
  - Cardiovascular disease
    - Beta-blockers and ACE inhibitors/ARBs
  - Arthropathy
Fast Facts
Full name: Leonid Ivanovych Stadnyk
Born: 1971 - 2014
Resides: Podoliantsi, Ukraine
Height: 8' 5.5"
Occupation: Farmer

Refused to be remeasured in 2009, so lost coveted title to: Sultan Kosen of Turkey; only 8’3’ tall
Sultan Kosen of Turkey; 8’3’ tall
#7. Which of the following statements regarding the tallest man that ever lived is FALSE?

A. His recorded height was 8’ 11’ tall
B. He worked in the same profession as Al Bundy (“Married with Children”)
C. He was born in Alton, Indiana
D. He wore size 37 ½ shoes
E. He died of septicemia
Robert Wadlow (1918-1940)
“The Alton Giant”

Normal size (8.5 lbs) at birth

Age 5  5’ 4”

Age 9  6’ 2” (discovered by *Time*)

Age 10 6’ 5” (210 lbs)

Age 11 6’ 7” (dx with pituitary gigantism)

Age 14 7’ 5” (301 lbs, tallest Boy Scout)

Age 16 7’ 10” (plagued by leg injuries)

Age 18 8’ 3” (attempted to attend college)

Age 19 8’ 5” (joined Ringling Brothers)

Age 22 8’ 11.1” (439 lbs) prior to death

The Tallest Man in History
Robert Wadlow
“The Alton Giant”

Born in Alton, Illinois in 1918
Diagnosed with pituitary abnormality at age 11
(surgery was deemed too dangerous)
Earned income as a pitchman for a shoe company
Had dreams of becoming a lawyer, but unable to function in college
Joined Ringling Bros side show, but refused to have his height augmented
Developed lower extremity cellulitis and died of sepsis in 1940
Robert Wadlow
“The Alton Giant”

In 1936
With siblings
Robert Wadlow
“The Alton Giant”

8 Feet 11.1” Tall
490 pounds
Summary

These growth disorders are rare but debilitating
While dwarfism and gigantism are clinically obvious, acromegaly may be more subtle
Identification of growth hormone excess early is amenable to treatment
Screen with IGF-1
Appropriate therapy can reverse morbidity and mortality
Association of skin tags, colon polyps and risk of colon cancer
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NPR’s *All Things Considered*, The Jewish Giant, 1999


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