

# Endocrine Issues that Affect Children with AGS

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Adapted from Children's Hospital of Philadelphia



# Abnormal Growth

- Meets 1 of the following 4 parameters:
  - Height < 2 standard deviations (SD) for population.
  - Height < 2SD below parental target height percentage.
    - Boy (cm):  $(\text{Father's Height} + \text{Mother's Height} + 13) / 2$
    - Girl (cm):  $(\text{Father's Height} - 13 + \text{Mother's Height}) / 2$
  - Height falling across major percentiles.
  - Slow growth velocity = <2 inches or 5cm per year between 3 years of age and puberty.



**GROWTH IS THE MOST  
SENSITIVE SIGN OF A  
CHILD'S OVER-ALL  
HEALTH.**

# Causes of abnormal growth in Alagille Syndrome

- Malabsorption
  - Liver disease
  - Pancreatic disease
- Heart defects
  - Especially those that cause cyanosis such as Tetralogy of Fallot
- Kidney disease
- Skeletal anomalies
  - Not likely a cause of abnormal growth
- Endocrine (hormonal)
- Genetic
  - The genetic cause itself results in abnormal genetic signaling resulting in abnormal height.

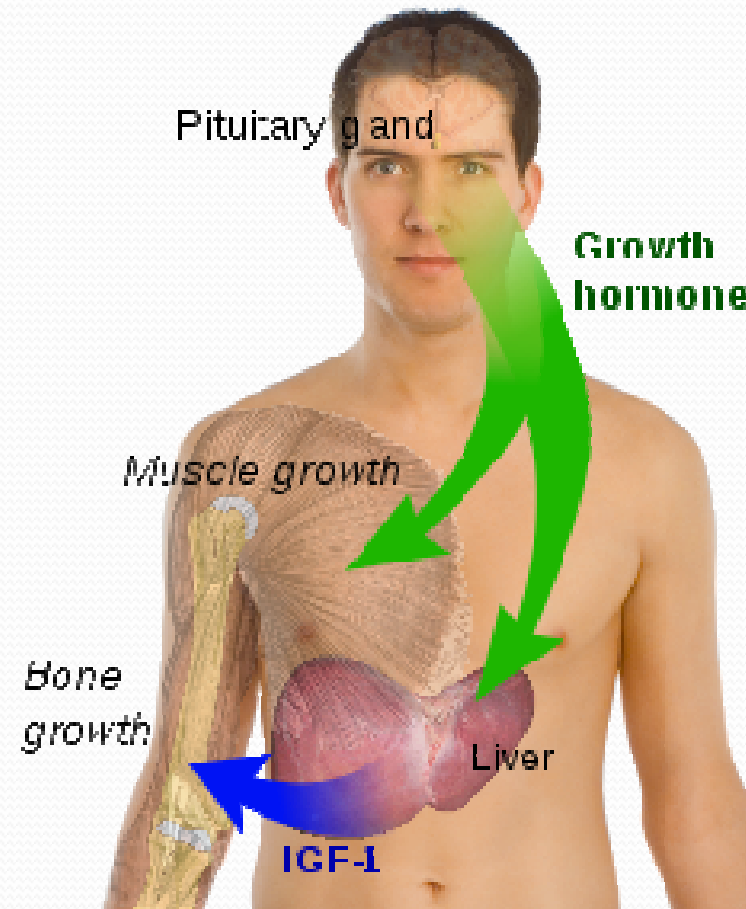


# Endocrine causes of growth failure

- Growth hormone resistance
- Hypothyroidism
- Hypogonadism

# Normal Growth Hormone Pathway

- Brain stimulates the pituitary gland to secrete growth hormone.
- Growth hormone binds to receptors in the liver.
- This results in production of IGF-1 that stimulates growth of bone at the growth plate.



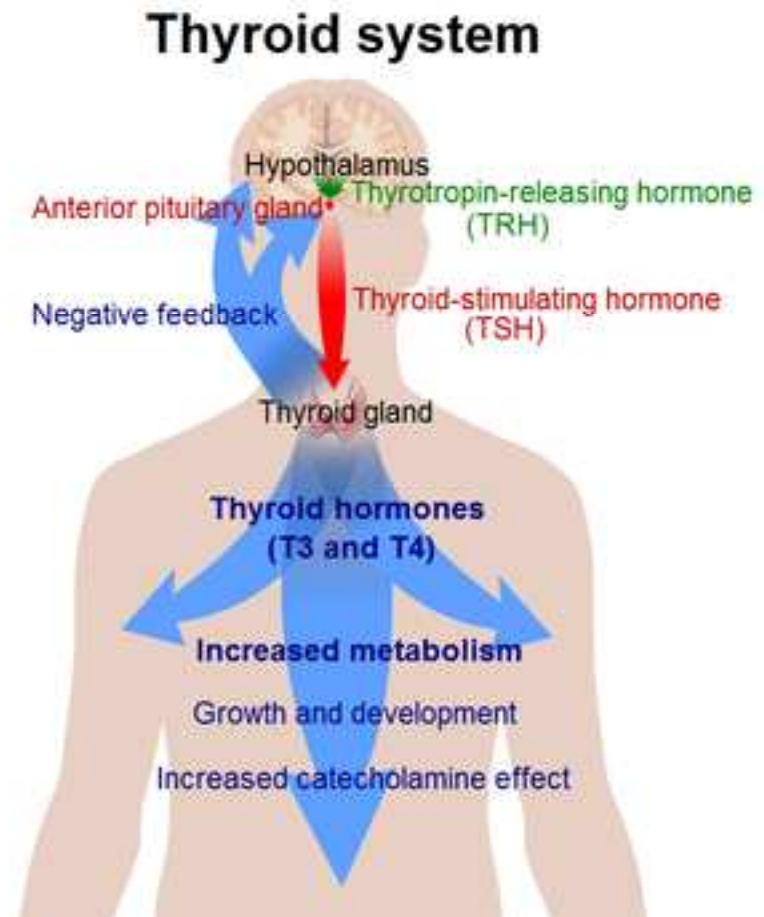


# Growth Hormone Resistance

- In AGS, growth hormone is normally released by the pituitary gland.
- However once it reaches the liver, it fails to bind properly to the appropriate receptor.
- This results in NOT stimulating the liver to produce IGF-1; therefore resulting in no signal at the growth plate in bone to grow.

# Normal Thyroid Signaling Pathway

- The brain stimulates the pituitary gland to release thyroid-stimulating hormone (TSH).
- TSH stimulates the thyroid to make and release thyroid hormone.
- Thyroid hormone plays integral role in metabolism as well as growth and development.





# Hypothyroidism

- The problem in AGS is primary hypothyroidism.
- This is where the brain normally stimulates the pituitary gland to produce TSH, but the thyroid gland is unable to make any thyroid hormone once stimulated by TSH.

# Hypothalamic-Pituitary-Gonadal Axis

- Brain stimulates pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- FSH and LH stimulate testicles and ovaries to produce sex hormones, testosterone/estrogen, respectively.
- Testosterone and estrogen are necessary for growth.

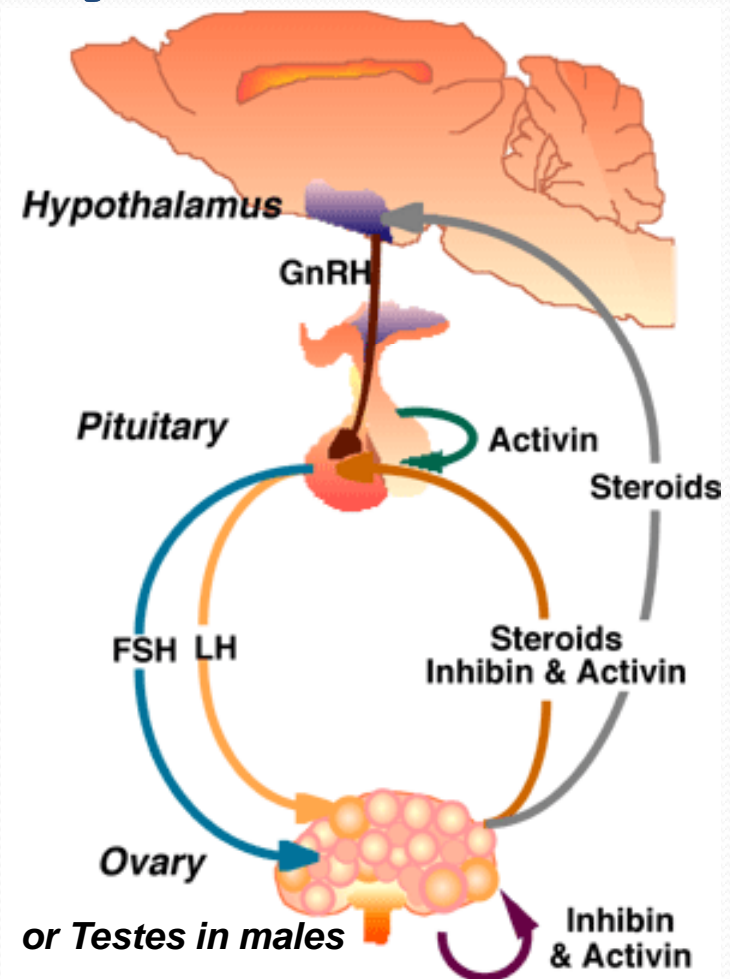


Figure 1: The Hypothalamic-Pituitary-Gonadal Axis



# Hypogonadism

- In patients with AGS, the brain stimulates the pituitary to release FSH and LH.
- However, the testicles and ovaries are unable to produce testosterone and estrogen, respectively.



# Endocrine Evaluation

- Skeletal maturity
  - Bone age (x-ray of left hand and wrist)
  - Determines skeletal maturity
- Growth hormone
  - IGF-I, IGFBP-3 is a random screen.
  - If above levels are low, then a provocative GH test/GH stimulation test is needed.
  - GH is normally secreted at night around 2 AM, so daytime measurements would not provide any good information.
- Hypothyroidism
  - Free T<sub>4</sub> and TSH
- Hypogonadism
  - Testosterone/estrogen and LH/FSH

# BONE AGE

- Gives assessment of growth potential left.
- Look at fingers, hands, and wrists beginning at the forearm.
- Look at growth plates
  - Open = Black = Cartilage
  - Fused = White = Bone
- Once fused, there is nothing further can be done to help growth.



# Treatment of endocrine causes of growth failure in AGS

- Growth hormone resistance
  - Potential treatment with rhIGF-1 (recombinant human IGF-1)
- Hypothyroidism
  - Treat with thyroid hormone – Synthroid
- Hypogonadism
  - Treatment with sex hormones (testosterone and estrogen)



# Normal growth rates during childhood

- Growth rates vary
  - Girls reach growth spurt before boys and stop growing before boys.
- Average male is 5 inches taller than the average female.
- Slow grower
  - Commonly seen in patients with chronic disease, such as patients with AGS.
  - May grow for a longer period of time.



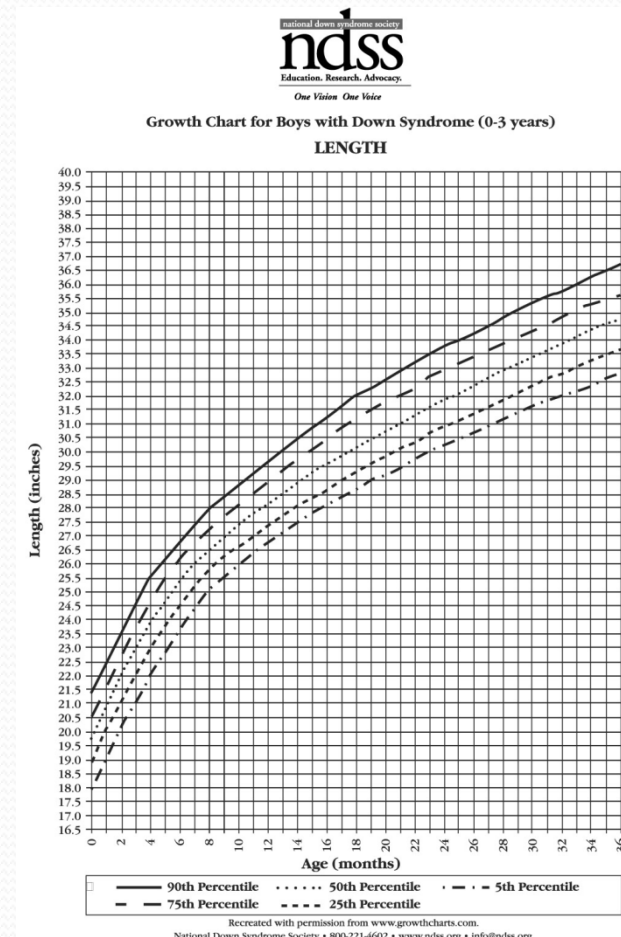
# Advocating for your child's growth

- Measured at least every well child visit.
  - Consistent technique.
- Plotted at every visit.
- Keep a copy of growth chart.
  - Share with specialists.
  - Bring to new pediatrician if change docs.
- If growth slows down, ask your doctor to aggressively investigate the cause.



# Syndrome-specific growth charts

- Down Syndrome is probably the best example.
- Example shows length from 0-3 months for boys.
- Available is complete set for boys and girls 0-18 years of age including head circumference charts in first 3 years of life.





# AGS specific growth charts

- Not yet available.
- Would be useful in evaluating in more appropriately evaluating the growth and development of children with AGS.



Thank you for your attention!!!  
Questions???