Pediatric Growth Disorders and Growth Hormone

Pediatric Growth Disorders and Growth Hormone

B. Michelle Schweiger, DO, MPH
Director, Pediatric Endocrinology
Department of Pediatrics

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Learning Objectives

At the end of this lecture, participants will be able to:

1. Discuss phases of normal growth for pediatric patients

2. Recognize, evaluate and treat the following conditions in children
   - ❑Constitutional growth delay
   - ❑Idiopathic short stature
   - ❑Chronic malnutrition with stunting of growth
   - ❑Growth hormone deficiency
   - ❑Small for gestational age
   - ❑Turner Syndrome

Phases of Normal Growth

- Intrauterine growth
  - occurs at a rate approximately 1.2 to 1.5 cm per week
  - Peaking at midgestation (18 weeks) 2.5 cm per week
  - Slowing to 0.5 cm just before birth

- Birth to 2 years
  - After birth rate of growth is most rapid-Peaking at 25 cm per year
  - The average length at birth for a term infant is 20 inches (50 cm)
  - Infants grow 10 inches (25 cm) during the first year of life
  - grow 4 inches (10 cm) between 12 and 24 months

- Toddlers
  - 3 inches (7.5 cm) between 24 and 36 months
  - 3 inches (7.5 cm) between 36 and 48 months
  - reach one-half of their adult height by 24 to 30 months

Cooke, Divall and Radovick. *Willliams Textbook of Endocrinology.* Philadelphia. Elsevier, 2011
Ball, Dains, Flynn,Solomon,Rosalyn W. Stewart. *Seidel's Guide to Physical Examination.* Elsevier, 2015
Boom, Duryea, Torchia. Normal growth pattterns in infants and prepubertal children UpToDate 2015.

Phases of Normal Growth

- Children
  - grow 2 inches/year (5 cm/year) between age four years and puberty
  - normal deceleration of height velocity before the pubertal growth spurt

- Puberty
  - Girls
    - Average age of pubertal growth spurt 10.5 years of age
    - Peak height velocity
      - during early puberty (Tanner stages II to III)
      - 6 to 10 cm/year
  - Boys
    - Average age of pubertal growth spurt 12.5 years
    - Peak height velocity
      - During mid-puberty (Tanner stages III to IV)
      - 5 to 11 cm/year

Cooke, Divall and Radovick. *Willliams Textbook of Endocrinology.* Philadelphia. Elsevier, 2011.
Ball, Dains, Flynn,Solomon,Rosalyn W. Stewart. *Seidel's Guide to Physical Examination.* Elsevier, 2015.

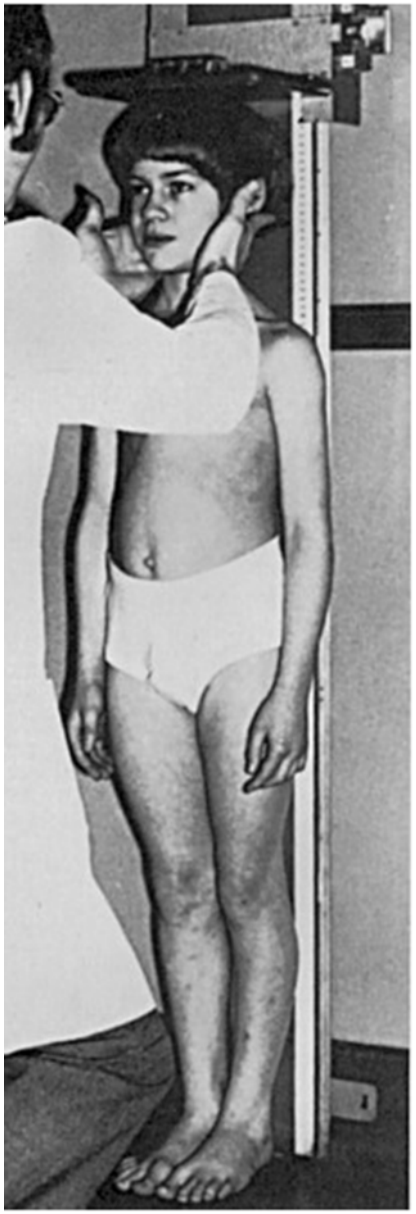
Weight gain

- First few days of life
  - may lose up to 10 percent of their birth weight
- By 10 to 14 days
  - Typically regain their birth weight
- Until three months of age
  - gain approximately 30 g/day (1 oz/day)
- Three and six months of age
  - gain approximately 20 g/day (0.67 oz/day)
- 6 and 12 months of age
  - 10 g/day
- Double their birth weight by four months of age
- Triple their birth weight by one year of age
- Children gain 2 kg/year (4.4 lbs/year) between two years and puberty
- *A prepubertal child whose weight velocity is <1 kg/year (<2.2 lbs/year) should be monitored closely for progressive nutritional deficits*

Cooke, Divall and Radovick. *Willliams Textbook of Endocrinology.* Philadelphia. Elsevier, 2011
Ball, Dains, Flynn,Solomon,Rosalyn W. Stewart. *Seidel's Guide to Physical Examination.* Elsevier, 2015.
Boom, Duryea, Torchia. Normal growth pattterns in infants and prepubertal children UpToDate 2015.

Measurement

- Child should be fully erect
- head in the Frankfurt plane
- Areas that should touch vertical axis of the stadiometer
  - back of the head
  - thoracic spine
  - buttocks
  - heels
- heels should be together.
- serial measurements should be made at the same time of day
- standing height may undergo diurnal variation.
- should be performed by a trained individual
- heights should be measured in triplicate
- variation should be no more than 0.3 cm
- mean height should be recorded.



Cooke, Divall and Radovick. *Willliams Textbook of Endocrinology.* Philadelphia. Elsevier, 2011.

Case # 1

- This is your first visit with Tina A. Small.
- She is a healthy 30 month old girl who was referred for evaluation of short stature.
- Mother is 4’11 and father is 5’6

What is your differential diagnosis for short stature

Differential Diagnosis for Short Stature

Normal Variants of Growth

- Familial short stature
- Constitutional growth delay
- Small for Gestational age

Endocrine causes of growth failure

- Hypothyroidism
- Cushing Syndrome
- Growth Hormone Deficiency

Genetic Diseases associated with poor growth

- Prader Willi Syndrome
- Turner Syndrome
- SHOX mutations
- Noonans syndrome

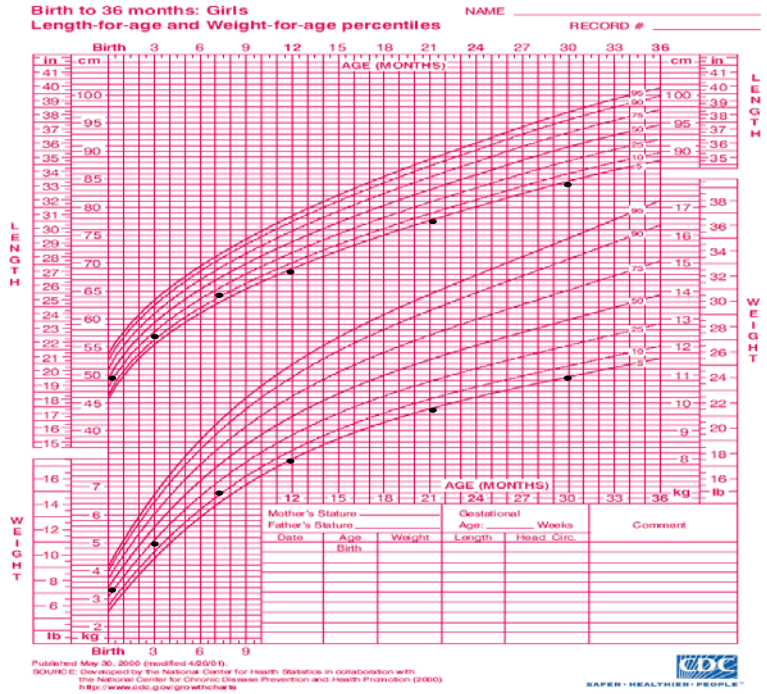
Systemic Disorders effecting growth

- **Undernutrition**
- Glucocorticoid therapy
- Gastrointestinal disease
  - Celiac disease
  - Crohns disease
- Rheumatologic disease
- Renal disease
- Cancer
- Pulmonary disease

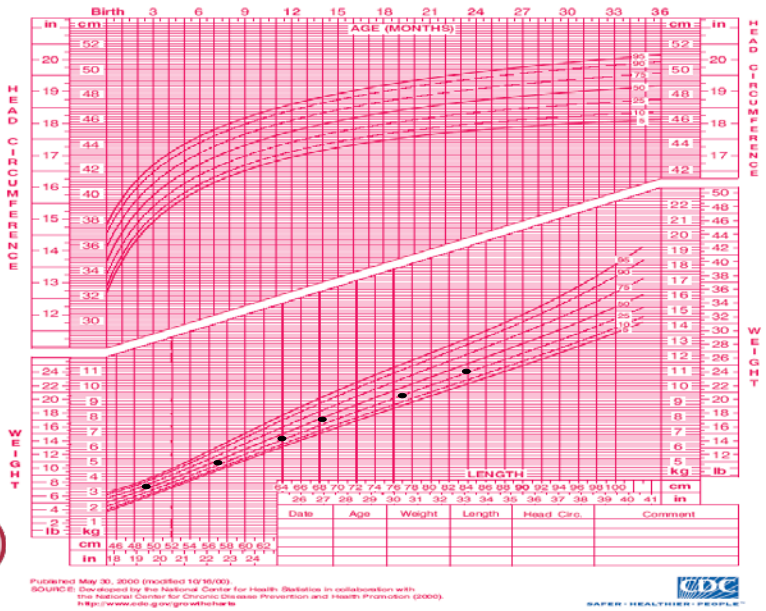
Skeletal Dysplasia

- Achondroplasia
- Osteogenesis Imperfecta
- Hypochondroplaisa

Case 1- chart a



Case 1 – chart b



- Mother 4'11(59 in) & Father 5'6 (66 in)
- MPH:In: (Father's Height - 5 + Mother's Height) / 2
- (66 in-5 + 59 in)/2=60 in

- During early infancy, height and weight both simultaneously decelerate, then stabilizes paralleling the normal growth curve

- Normal growth velocity

- Normal weight for length

- Normal bone age

- Child's height percentage consistent with midparental height percentile

- What is your diagnosis?
- *Familial (genetic) short stature*

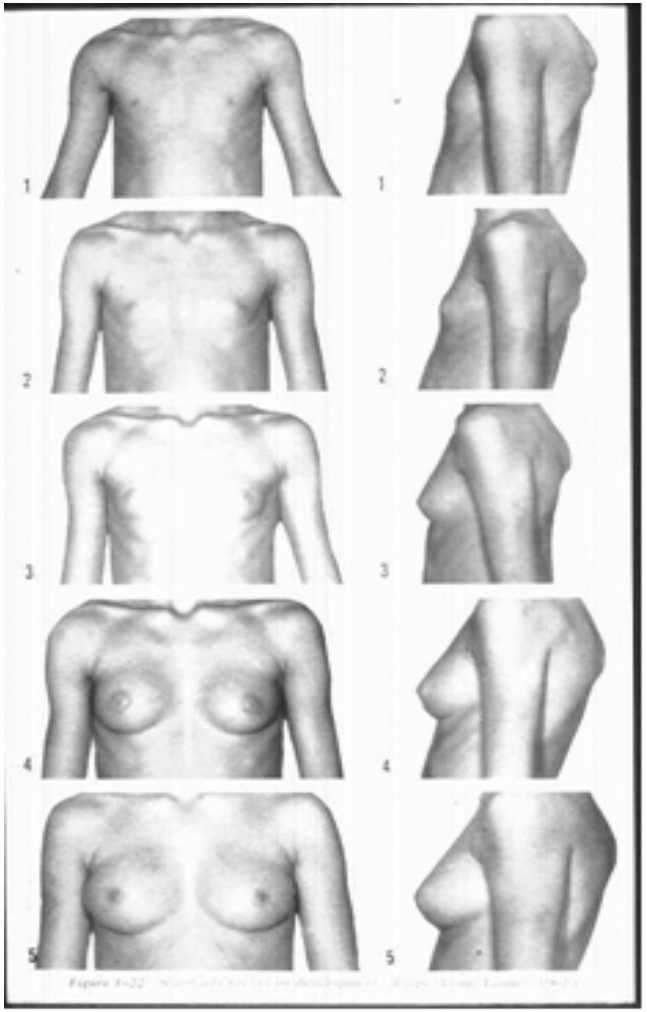
Case #2

- This is your visit with Tina C. Small
- She is a healthy 30 month old girl who was referred for evaluation of short stature.
- Mother had menarche at age 11. Father stopped growing after high school
- Tina C. Small returns at age 13 year for poor growth
- She just developed breasts (tanner II). She has no acne, no axillary hair, no pubic hair, and no menses

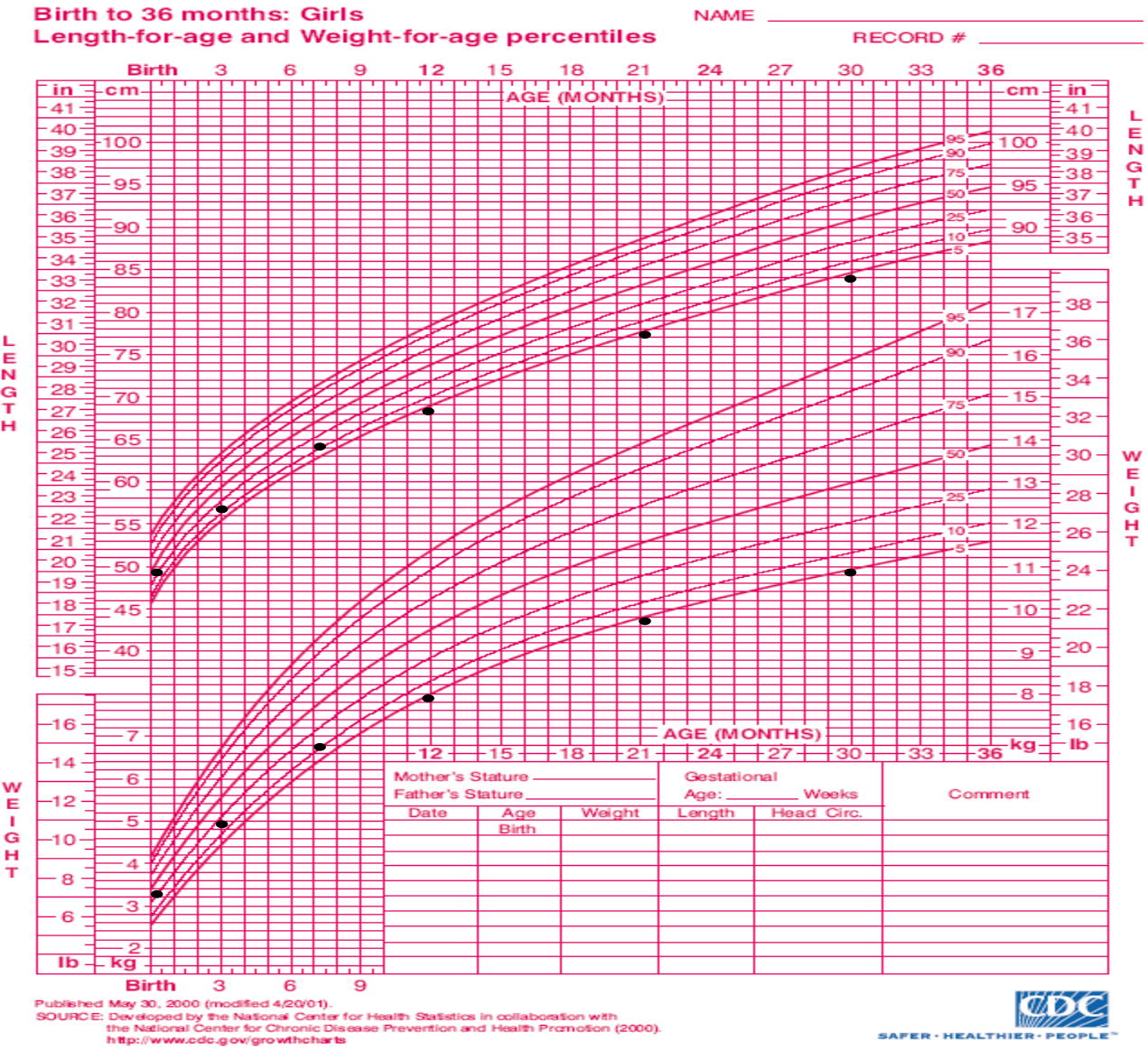
What is the average age for pubertal development for females?

- Breast buds tanner stage II
  - –Avg. 10.9 years
- Growth acceleration
  - –peak prior to menarche)
  - – Avg. 12 years
- Menarche
  - –usually 1½-2 years after onset of puberty
  - – Avg. 12.7 years

So Tina's pubertal development is delayed

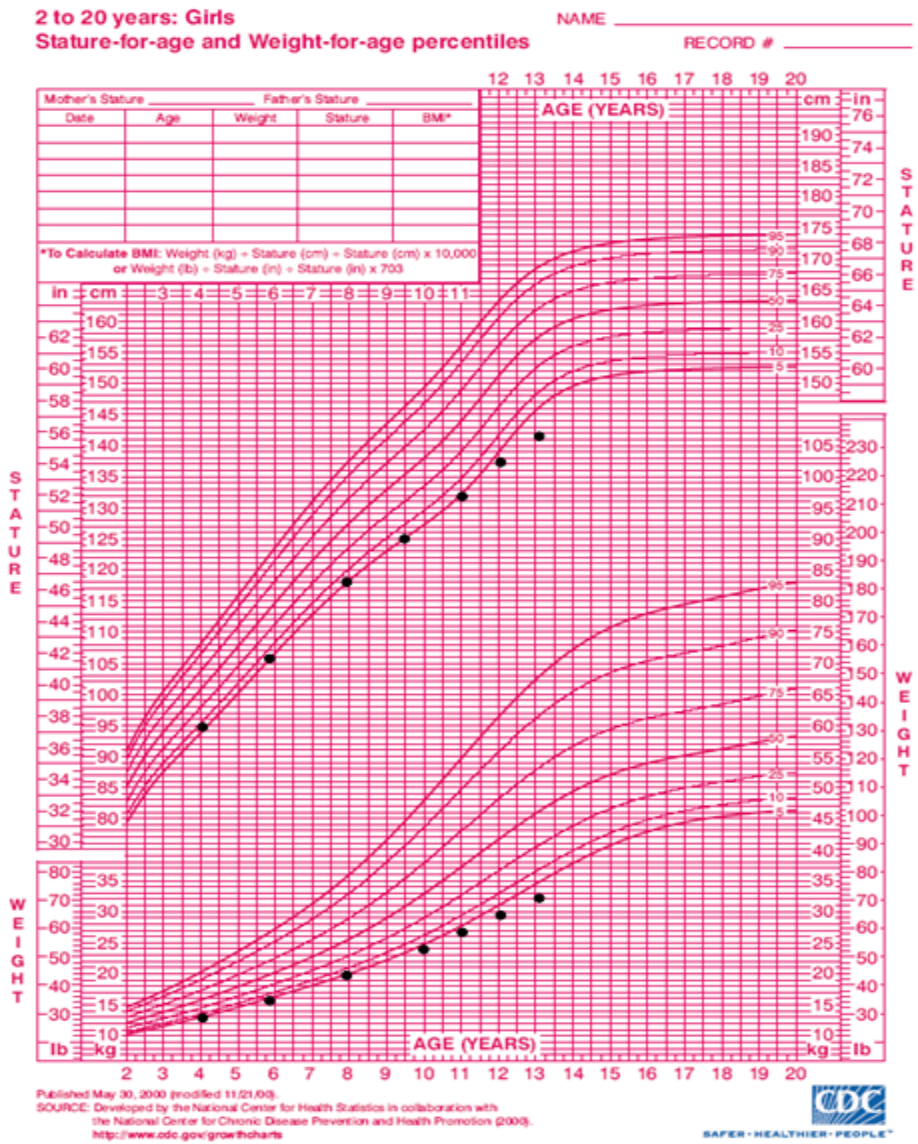


Growth Chart at 30 months of age



- During early infancy height and weight both simultaneously decelerate
- Then stabilizes paralleling the normal growth curve

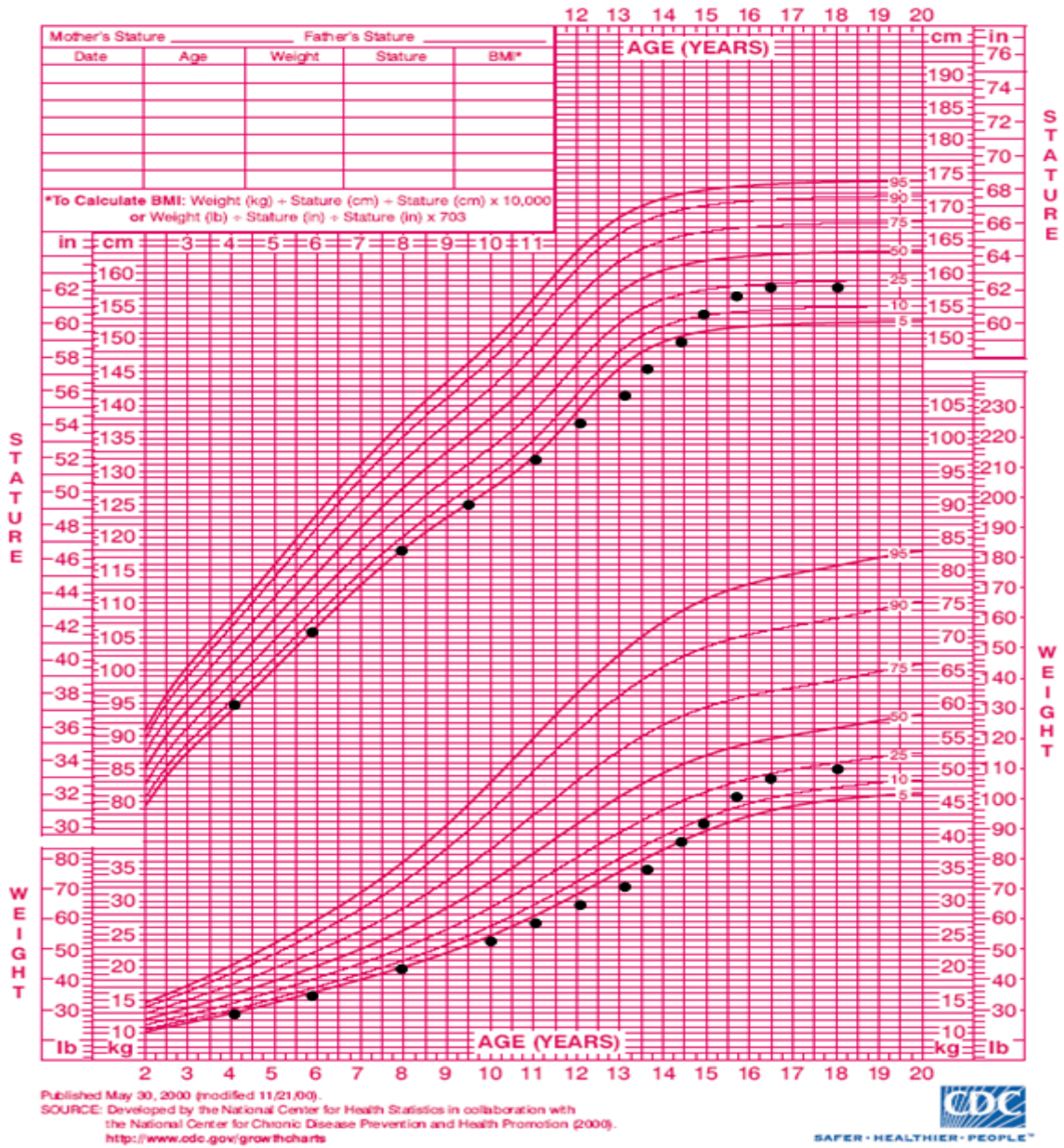
Growth Chart at 13 years of age



- Normal growth rate
- Normal to low normal BMI

What is your diagnosis?

Constitutional growth delay


2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
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Idiopathic Short Stature

- Diagnosis of exclusion[1]

- Healthy short children with no identified etiology for poor growth[1]
  - No systemic illness
  - No endocrine disorders
  - No genetic syndromes
  - No bone dysplasias
  - No SGA

- By definition these children are > 2.25 SD below the mean in height and are unlikely to catch up in height[2]
  - <63 inches for boys
  - < 59 inches for girls

- Comprise nearly 80% of the short children who present to a pediatric clinic [3]

Cohen P, et al. *JCEM, (93): 4210-4217,2008*[1]
Wilson et al. *J Pediatr (43): 415-21, 2003*[2]
Kappy et al. *Pediatric Practice Endocrinology*, Mc Graw Hill Medical, 2010.[3]

Idiopathic Short Stature (ISS)

- The mean increase in adult height in children with ISS with growth hormone therapy (average duration 4-7 yr) is 1.5-3 inches[1-2]

- Combined therapy with GnRH analog plus growth hormone in central precocious puberty.
  - 7.9 +/- 1.1 cm in patients treated with GH combined with GnRH analogue
  - patients treated with GnRH analogue alone the gain was just 1.6 cm +/- 1.2 (p=0.001)[3]

- Aromatase inhibitors
  - Reduce conversion of androgens to estrogen
  - Limit estrogen induced growth plate closure
  - Randomized, placebo-controlled, multicenter trial reports of 4-6 cm gain in near final height when used with growth hormone[4]

Wit JM et al. Pediatr Res, (53), 154, 2003[1]
Wilson et al. J Pediatri (43) 415-21, 2003[2]
Pucarelli et al. JPEM, (1), 811-20, 2000[3]
Mauras et al. JCEM, 93(3):823-31,2008[4]

Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

Ellen Werber Leschek, Susan R. Rose, Jack A. Yanovski, James F. Troendle, Charmian A. Quigley, John J. Chipman, Brenda J. Crowe, Judith L. Ross, Fernando G. Cassorla, Werner F. Blum, Gordon B. Cutler, Jr., Jeffrey Baron, and on behalf of the National Institute of Child Health Human Development-Eli Lilly and Company Growth Hormone Collaborative Group

Address all correspondence and requests for reprints to: Jeffrey Baron, M.D., National Institutes of Health, Building 10, Room 10N262, 10 Center Drive, MSC 1862, Bethesda, Maryland 20892-1862. E-mail: jeffrey_baron@nih.gov.

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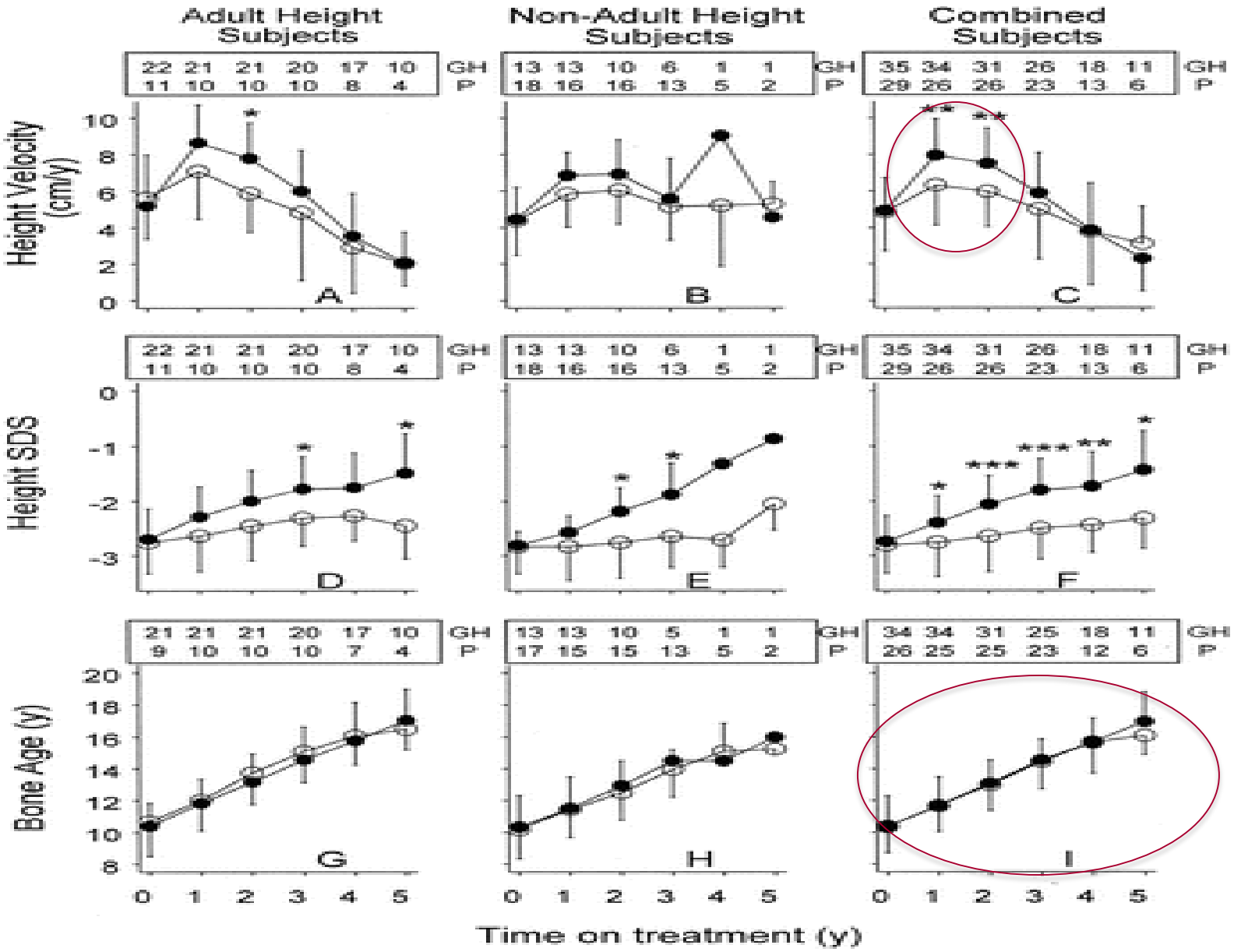
Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

- Randomized double blind placebo controlled study
- N-68; 53 male and 15 females
- Idiopathic short stature (height or predicted height < -2.5 SD score)
- GH 0.074 mg/kg) or placebo sq three times per week until near adult height
- At study termination adult height available 33 patients
- Mean duration of treatment 4.4 years
- Adult height was greater in GH-treated group than in the placebo-treated group by 0.51 SDS (3.7 cm; P < 0.02; 95% confidence interval

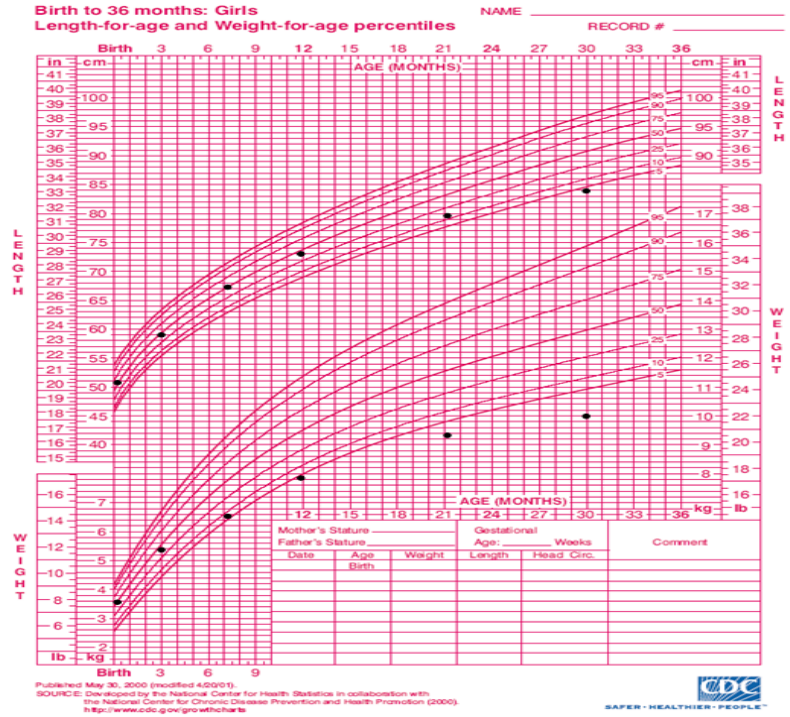
Leschek et al. JCEM, 89(7) 3140-3148, 2004

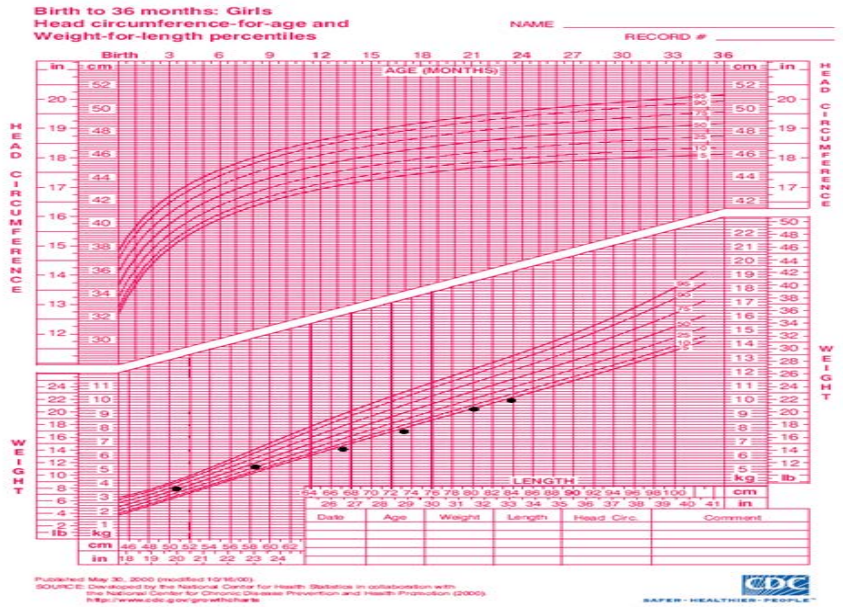


Leschek et al. JCEM, 89(7) 3140-3148, 2004

Case # 3

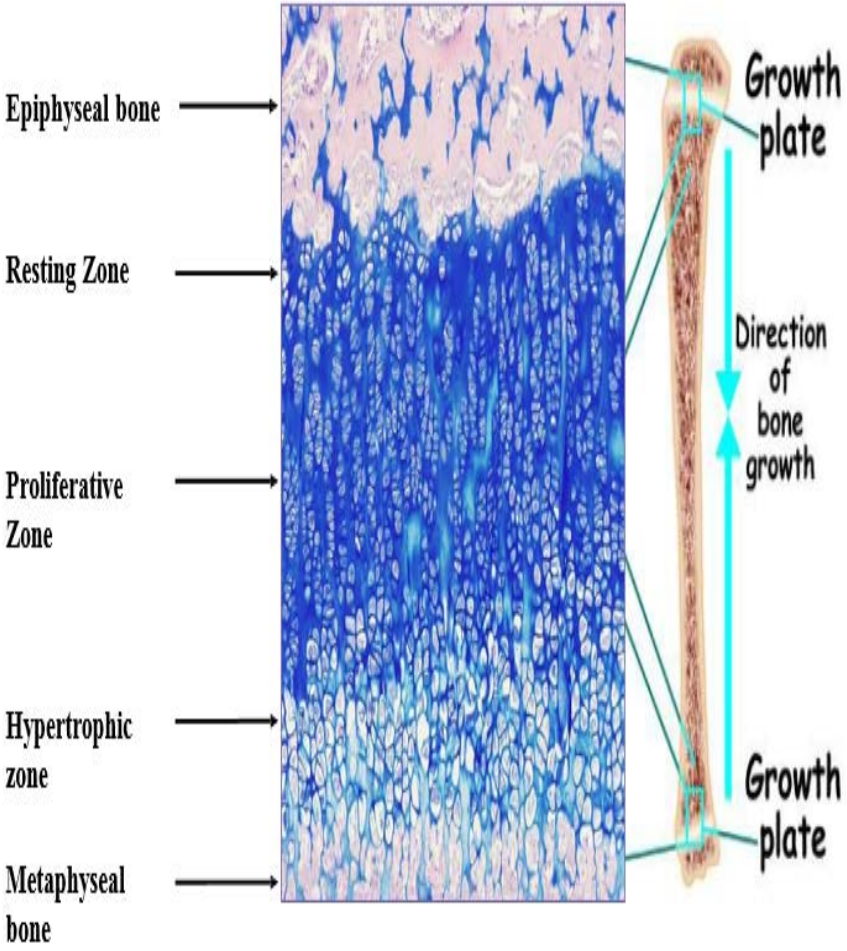
- This is your first visit with Tina B. Small.
- She is a 30 month old girl who was referred for evaluation of short stature.
- She has a poor appetite and is a picky eater.
- Mother is 5’4” and father is 5’10”.
- Work up reveals delayed bone age





- First weight decelerates, then height decelerates
- Decreased weight for length
- Low BMI
- What is your diagnosis?

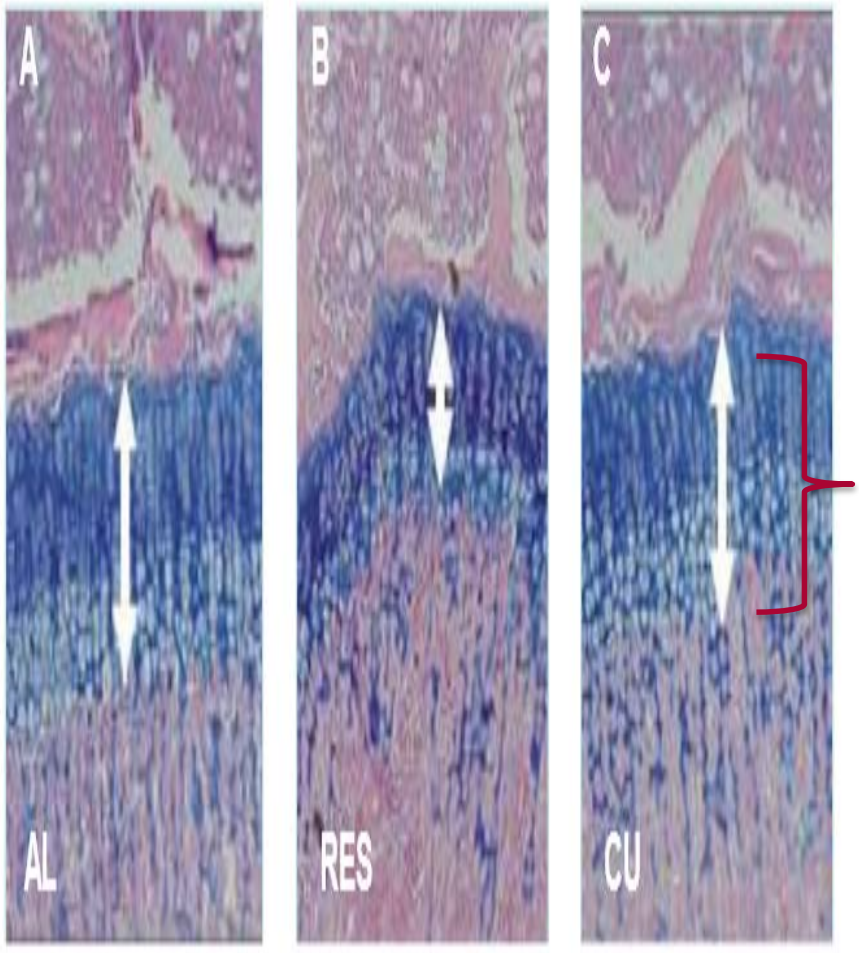
Chronic malnutrition with stunting of growth



Epiphyseal growth plate of male Sprague Dawley rat (34 days old) stained with hematoxylin/eosine/Alcian Blue. Magnification, 100×. The different zones of the growth plate are marked.

- Malnutrition is considered a leading cause of growth attenuation in children [1]
- Spontaneous catch up growth usually occurs once food is replenished[1]
- Children with marasmus and kwashiorkor have significantly lower height than healthy subjects[2]
- Children with eating disorders from developed countries were on average shorter than controls[3]
- ***Good nutrition ensures proper "building blocks" for growth***

Gat-Yablonski, Nutrients (7), 517-551, 2015[1]
Kilic et al. Clin Biochem, (37), 382-387[2]
Favaro et al. Int J. Eat. Disord, (40), 549-553,2007[3]



Effect of food restriction and re-feeding on the height of the EGP.

- Twenty-four-day-old male SD rats were allowed to eat
  - –AL-ad libitum
  - –RES- subjected to 40% food restriction for 11 days
  - –CU- subjected to 10 days of food restriction followed by one day of re-feeding[1]

Epiphyseal growth plate (EGP)

  - –Food restricted rats gained 1.2 g/day
  - –Ad lib rats 6.5 g/day
  - –When food restriction removed rats had largest increase (15.1 g) on the first day[1]
  - –Bone length increased seven days later[2]

Gat-Yablonski, *Nutrients* (7), 517-551, 2015[1]
Even-Zohar. *Bone* (42), 505-515,2008

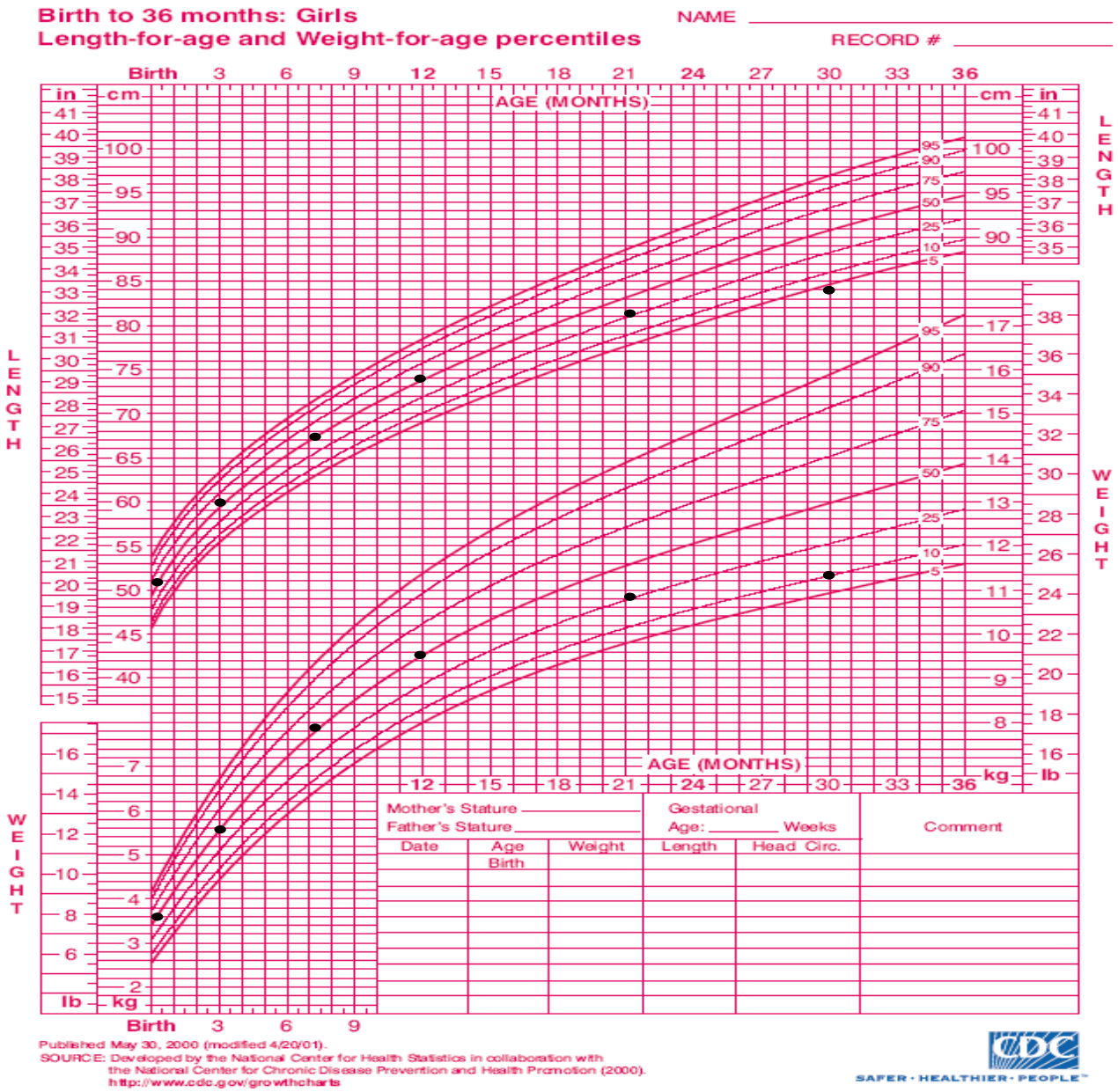
Hormone	Affected by food restriction	Effect on Growth
· Insulin	· Reduced	· Stimulates growth
· Growth hormone	· Increased	· Stimulates growth
· Insulin like growth factor	· Reduced	· Stimulates growth
· Glucocortiocoids	· Increased	· Inhibits growth
· Leptin	· Reduced	· Stimulates growth
· Thyroid hormones	· Reduced	· Stimulates growth
· Sex hormones	· Reduced	· Stimulates growth

Gat-Yablonski, Nutrients (7), 517-551, 2015

Case # 4

- This is your first visit with Tina D. Small.
- She is a 30 month old girl who was referred for evaluation of short stature.
- Her parents note that she has not been growing.
- Mother is 5’5” and father is 5’9”
- She brings an outside bone age which is delayed

Case 4



Simultaneous deceleration of both height and weight

Normal or increased weight for length

Low growth velocity

Case # 4 continued

What is your differential diagnosis?

Growth hormone deficiency, acquired hypothyroidism, or occult disease

What work up do you recommend?

basic metabolic panel, complete blood count, TSH, T4, insulin like growth factor 1, insulin like growth factor binding protein 3, sedimentation rate, tissue transglutaminase IgA

All normal except low IGF 1 and IGF BP3, patient also fails formal growth hormone testing

Diagnosis growth hormone deficiency

History of Growth Hormone

- 1956
  - First human to receive GH therapy of bovine origin
  - Given for 3 weeks for metabolic balance studies revealing no effects[1]
- 1958
  - Human GH (hGH) was first prepared and studied by Raben
  - Shown to produce growth in sexually undeveloped adolescent[2]
- 1959
  - Retrieved HGH from human pituitaries given to presumed GHD patients
  - 1 mg hGH was needed to treat one patient per day
  - > 360 mg of hGH needed per patient per year
- 1963
  - Immunoassay for hGH became available
- 1985
  - Synthetic GH became available

Blizzard, Indian J Pediatri 2012 79 (1): 87-91[1]
Raben MS. JCEM, 1958; 18:901-3[2]

Key History and Physical Examination Findings Indicating Growth Hormone Deficiency can be Present

- Neonate with
  - Hypoglycemia
  - Prolonged jaundice
  - Microphallus
  - Traumatic delivery
- Cranial irradiation
- Head trauma
- Central nervous system infection
- Consanguinity
- Craniofacial midline abnormalities
- Severe short stature < -3 SD
- A height velocity below -2 SD over 1 year
- A height velocity morethan 1.5 SD below the mean sustained over 2 years
- Signs of multiple pituitary hormone deficiency
- Signs indicative of intracranial lesion

Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH research society. J Clin Endocrinol Metab. 2000, 85: 3990-3993[1]

Kappy et al. Pediatric Practice Endocrinology, Normal Growth and Growth Disorders, 56[2]

Brain Magnetic Resonance Imaging as First –Line Investigation for Growth Hormone Deficiency Diagnosis in Early Childhood

- Retrospective cohort 68 children diagnosed with growth hormone deficiency (GHD) before 4 years of age
  - –43 boys & 25 girls
  - –1998-2012
- Diagnosis established by pharmacological GH stimulation tests
  - –Exception of newborns with clinical signs of GHD
- Results37 children were diagnosed with isolated GHD and 31 with multiple pituitary hormone deficiency (MPHD)
- Prevalence of abnormal MRI in whole cohort was 91.2%
- All patients diagnosed during the first 2 years of life had abnormal MRI findings
  - –Prevalence of complex defects
    - First year of life- 94.1%
    - Second year of life-75%
- Brain MRI may represent first-line investigation for diagnosing GHD in infancy and early childhood

Pampanini et al. Horm Res Paediatr 2015;84:323–330

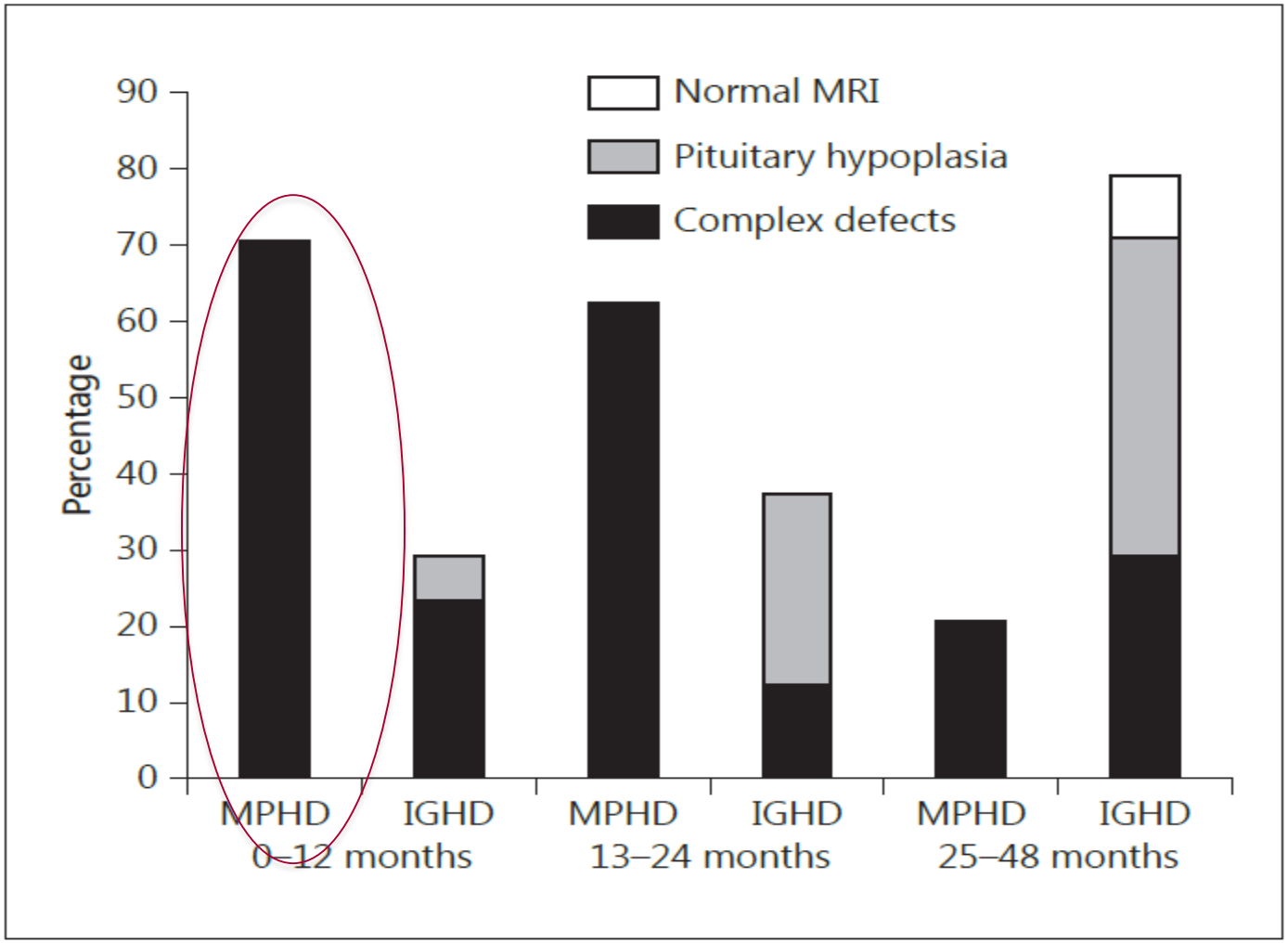


Fig. 1. Age distribution of the different MRI findings in children with either IGHD or MPHD.

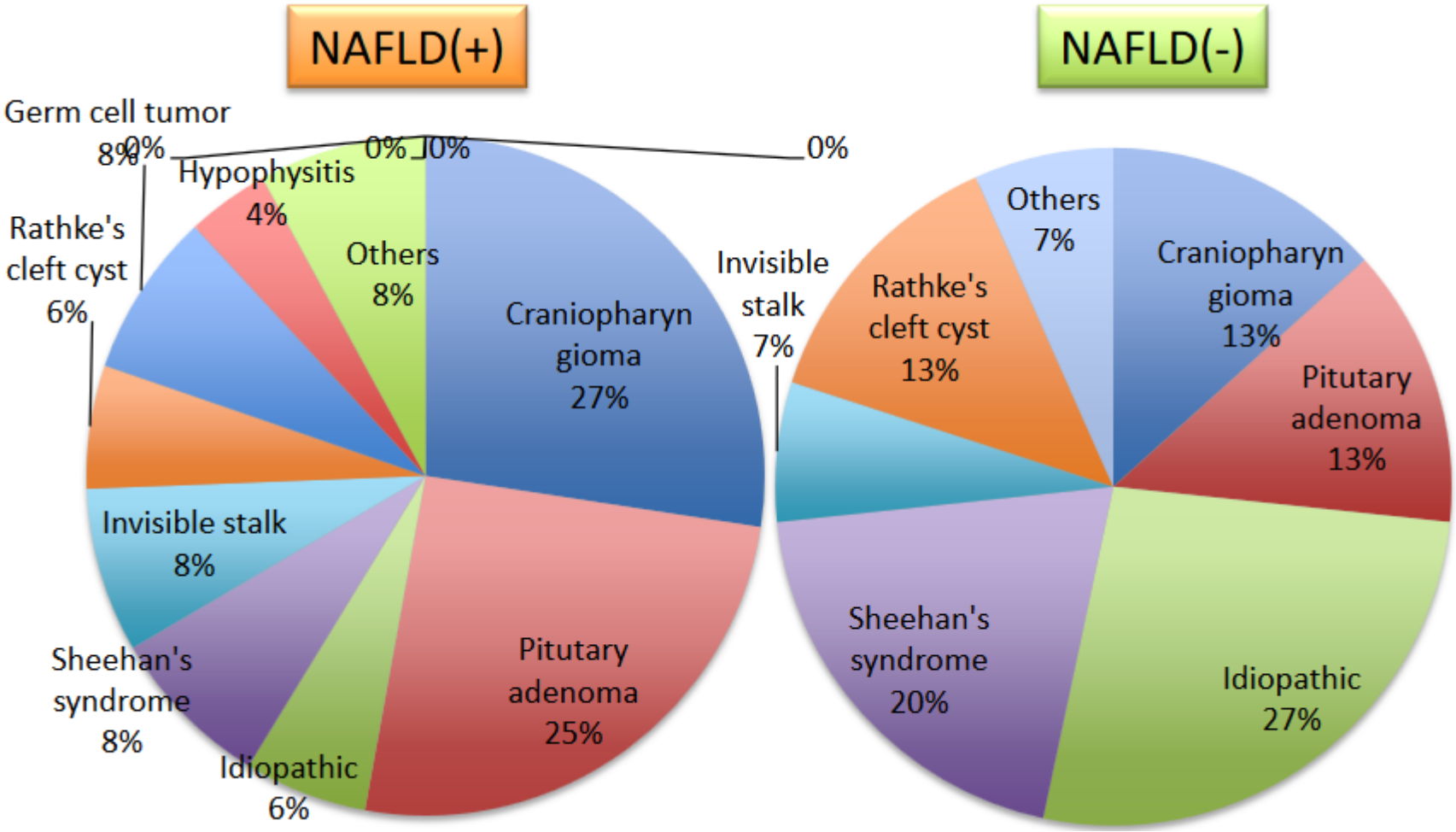
Pampanini et al. Horm Res Paediatr 2015;84:323–330

Nonalcoholic fatty liver disease in adult hypopituitary patients with Growth Hormone deficiency and the impact of Growth Hormone Replacement Therapy

- 69 Japanese adult hypopituitary patients with GHD
- The prevalence of NAFLD in hypopituitary patients with GHD was significantly higher than in controls (77% vs 12%, P<0.001)
- Of 16 patients assesses by liver biopsy
  - 14 (21%) were diagnosed with NASH
- GH replacement therapy
  - significantly reduced serum liver enzyme concentrations
  - Improved histological changes in the liver
  - Reduction of fibrotic marker concentrations in patients with NASH

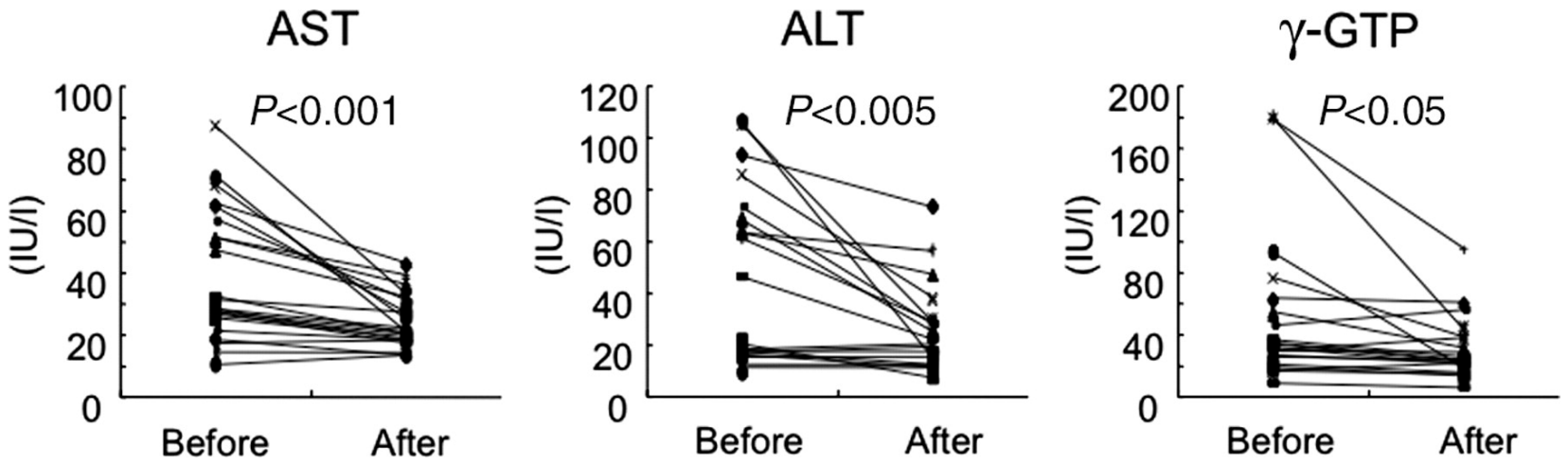
Hitoshi Nishizawa et al. Eur J Endocrinol 2012;167:67-74

Causes of pituitary deficiency in the patients with or without NAFLD



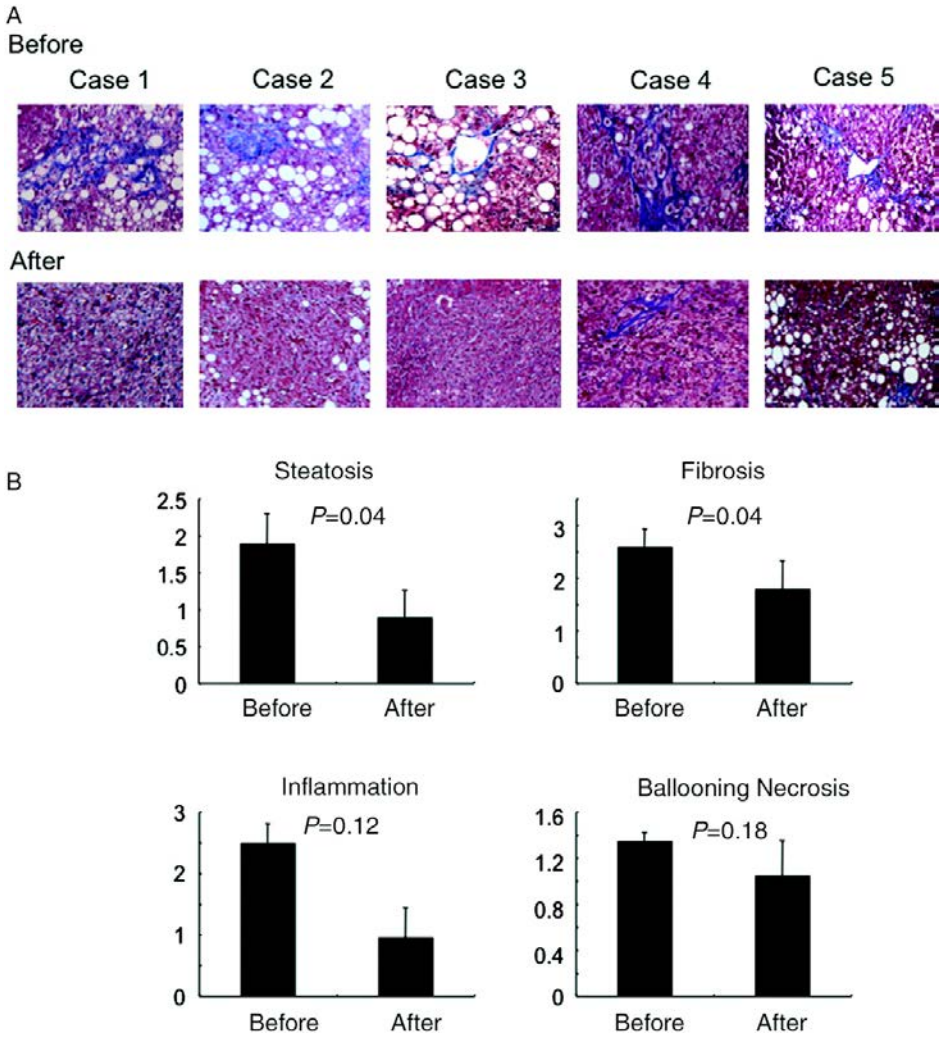
Hitoshi Nishizawa et al. Eur J Endocrinol 2012;167:67-74

Figure 1 Serum aspartate aminotransferase and alanine aminotransferase, and γ-GTP concentrations before and after GH replacement therapy for 6 months in adult patients with GHD.



Hitoshi Nishizawa et al. Eur J Endocrinol 2012;167:67-74

Figure 3 (A) Histological analysis by Masson's trichrome staining of the liver before and after GH replacement therapy in NASH patients with GHD (cases 1–5 in Table 2).



Hitoshi Nishizawa et al. Eur J Endocrinol 2012;167:67-74

Laron Syndrome (LS)
Primary Growth Hormone Resistance or Insensitivity

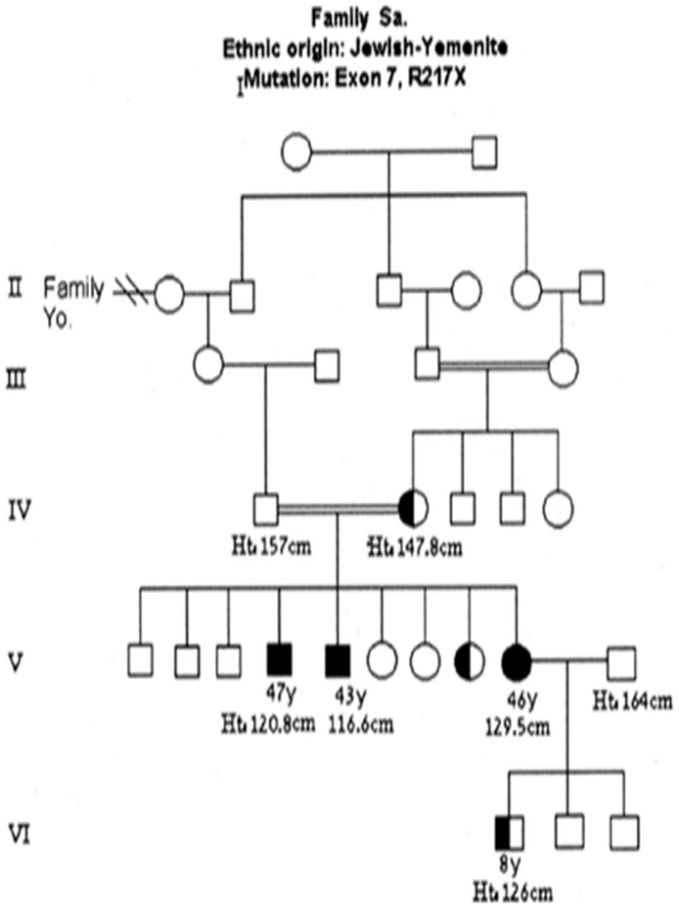
- 3 sibling with marked short stature were evaluated by Dr. Laron in 1958
- Resembled children with hypopituitarism

• Boy is 3.5 years and the girl is 1.5 years old

Laron Z· **Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003.**J Clin Endocrinol Metab. 2004 1031-44.

Laron Syndrome (LS) Inheritance

- Consanguineous Jewish family of Yemenite origin
  - Parents grandparents were first cousins
- Five older siblings of normal stature

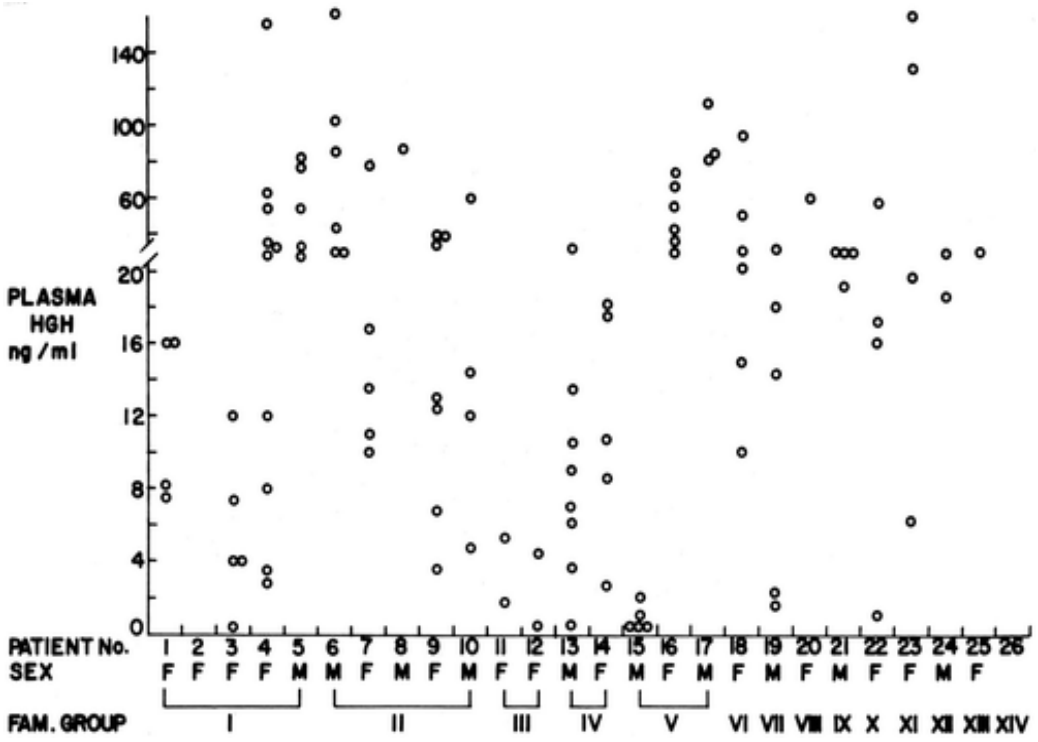


- Laron later found that almost all the patients belonged to consanguineous families
- Conclusion that LS is caused by fully penetrant autosomal recessive mechanism

Laron et al. Consequences of not treating children with Laron syndrome (primary growth hormone insensitivity). J Pediatr Endocrinol Metabol: 1243-1248, 2001.

Laron Syndrome and Hormone Profile

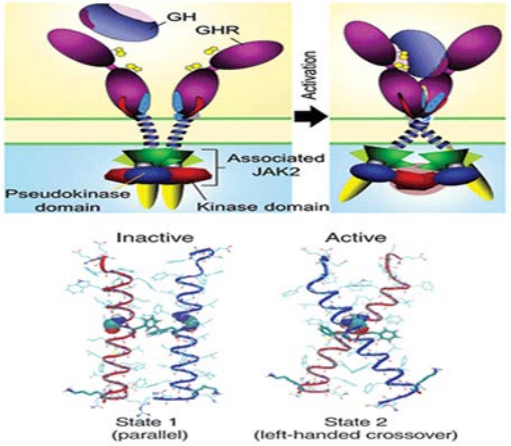
- Overnight fasting GH levels are high
- Nocturnal pulses reach 200-300 ng/ml
- Pituitary gland not enlarged
- Serum IGF 1 is undetectable
- No rise with hGH

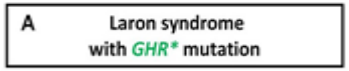


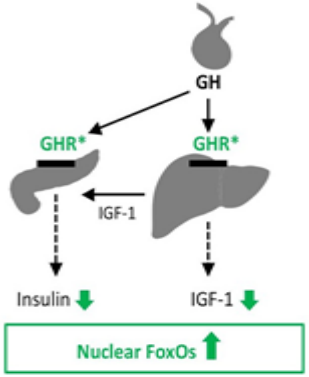
Laron Z. **Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003.** J Clin Endocrinol Metab. 2004 1031-44.

Laron Syndrome (LS)
Primary Growth Hormone Resistance or Insensitivity

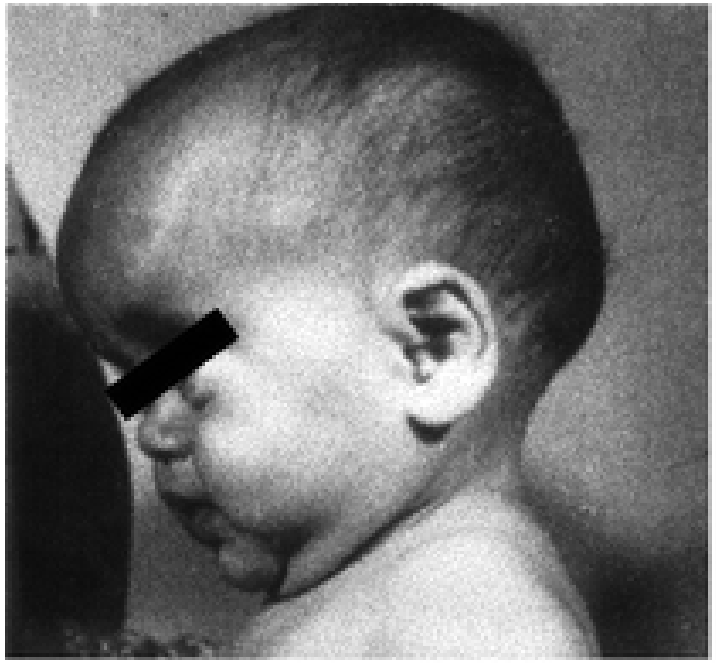
- In 1984 biopsied liver of two patients
- Showed that ^{125} IhGH does not bind to GH-Rs
- Found molecular defects residing in growth hormone receptor
  - Majority in extracellular domain of the receptor
  - Exons 2-7 and introns
  - Results in absence of circulating GH binding protein
- Inability of IGF 1 regeneration
- Since then several hundred cases discovered worldwide
- Majority of cases from the Mediterranean or from Ecuador

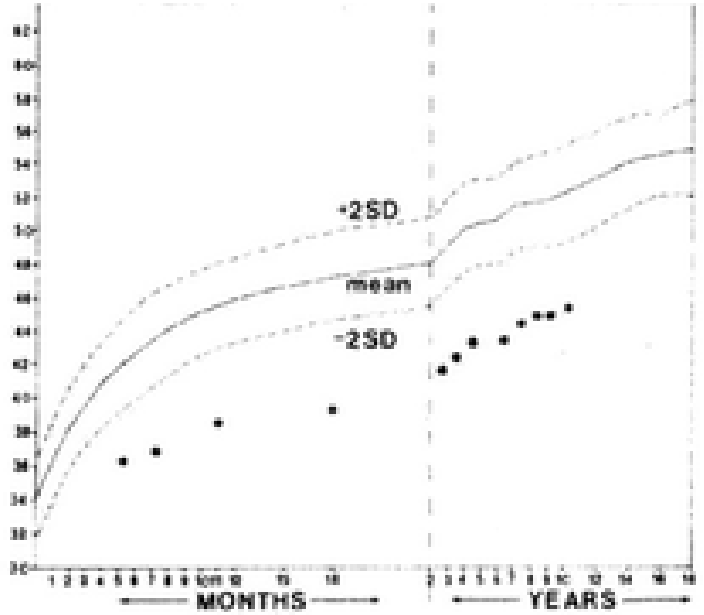


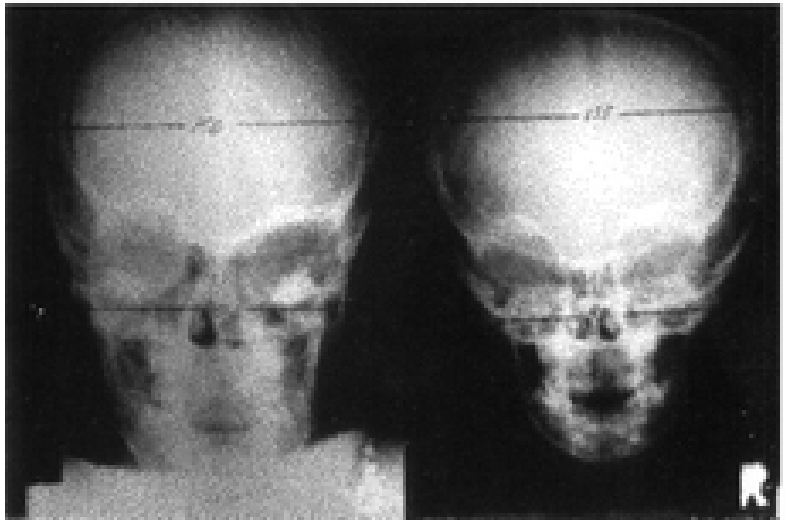


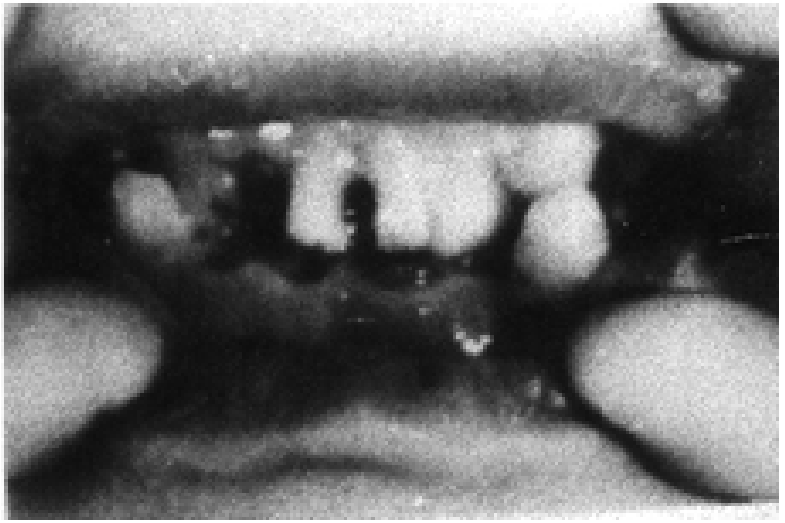


Laron Z et al. Gentic pituitary dwarfism with high concentration of growth hormone. A new inborn error of metabolsim? Isr J Med Sci, 1966, 153-155.

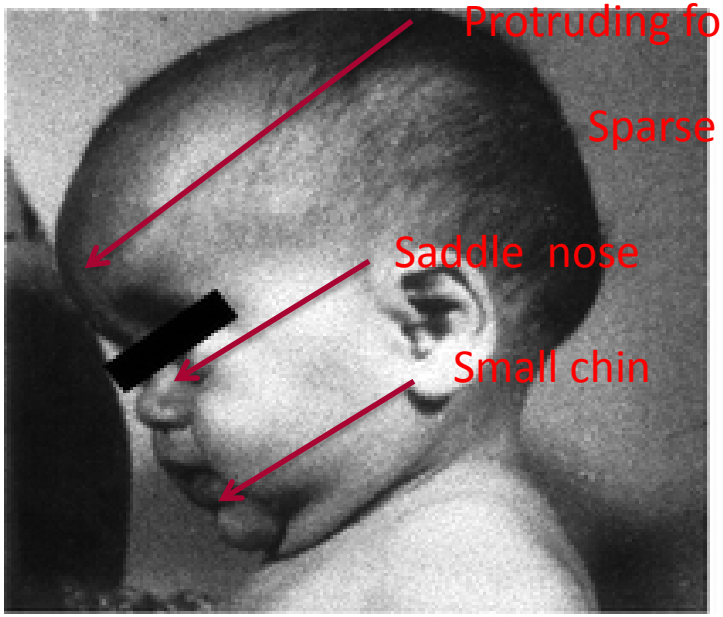




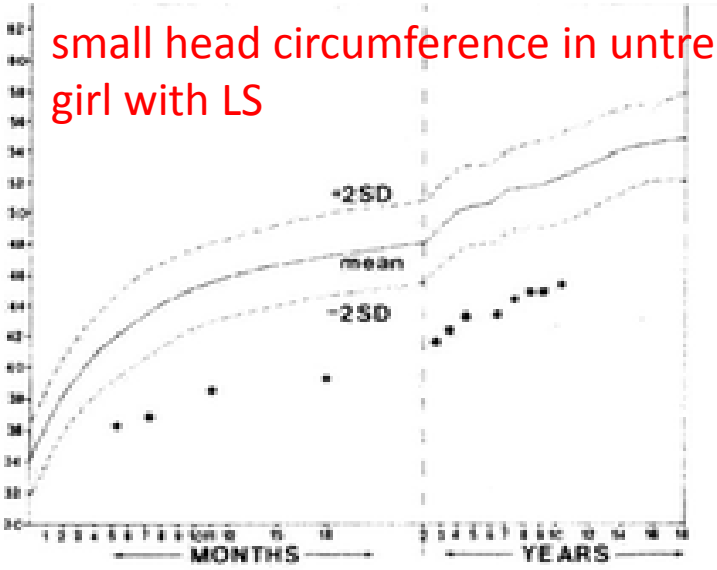


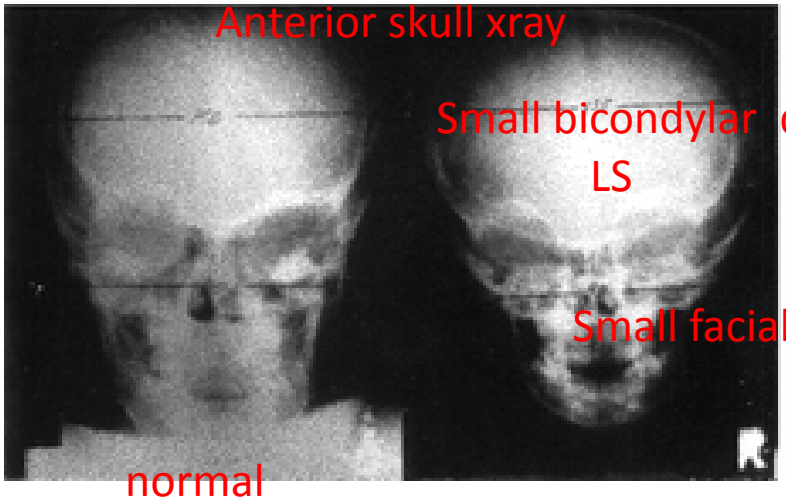


Laron Z. **Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003.** J Clin Endocrinol Metab. 2004 1031-44



small head circumference in untreated girl with LS





Laron Z, *JCEM*, 1031-44, 2004

Treatment Laron Syndrome

- Final heights range 116 and 142 cm males
- 108 and 136 cm in females
- Recombinant biosynthetic IGF 1 available since 1986
  - First year of growth the most
  - Growth velocity not as intense as that of GH

Laron et al. *Acta Endocrinol* 121: 603-608, 1989

FDA-Approved Conditions for the Use of Growth Hormone Therapy for Short Stature

Condition	Year approved by FDA
Childhood growth hormone deficiency	1985
Chronic renal insufficiency	1993
Turner syndrome	1997
Prader-Willi syndrome	2000
Born small for gestational age	2001
Idiopathic short stature	2003
SHOX gene deficiency	2006
Noonan syndrome	2007

FDA = US Food and Drug Administration.

FDA-Approved Indications for Growth Hormone Therapy

Indication	Dosage
Growth Hormone Deficiency	0.16-0.3 mg/kg/wk
Prader Willi Syndrome	Up to 0.24 mg/kg/wk (or body surface area-based dosing at 1 mg/m2 BSA/day)
SGA/IUGR	Up to 0.48 mg/kg/week
Turner Syndrome	Up to 0.33-0.47 mg/kg/week
Noonan Syndrome	Up to 0.066 mg/kg/day
Idiopathic Short Stature	Up to 0.47 mg/kg/week
Shox Deficiency	Up to 0.35 mg/kg/wk

Kappy, Allen, Geffner (2010) Normal growth and Growth Disorders, Pediatric Practice endocrinology. Page 42. Mc Graw Hill Medical.

Adverse events associated with Growth Hormone Therapy

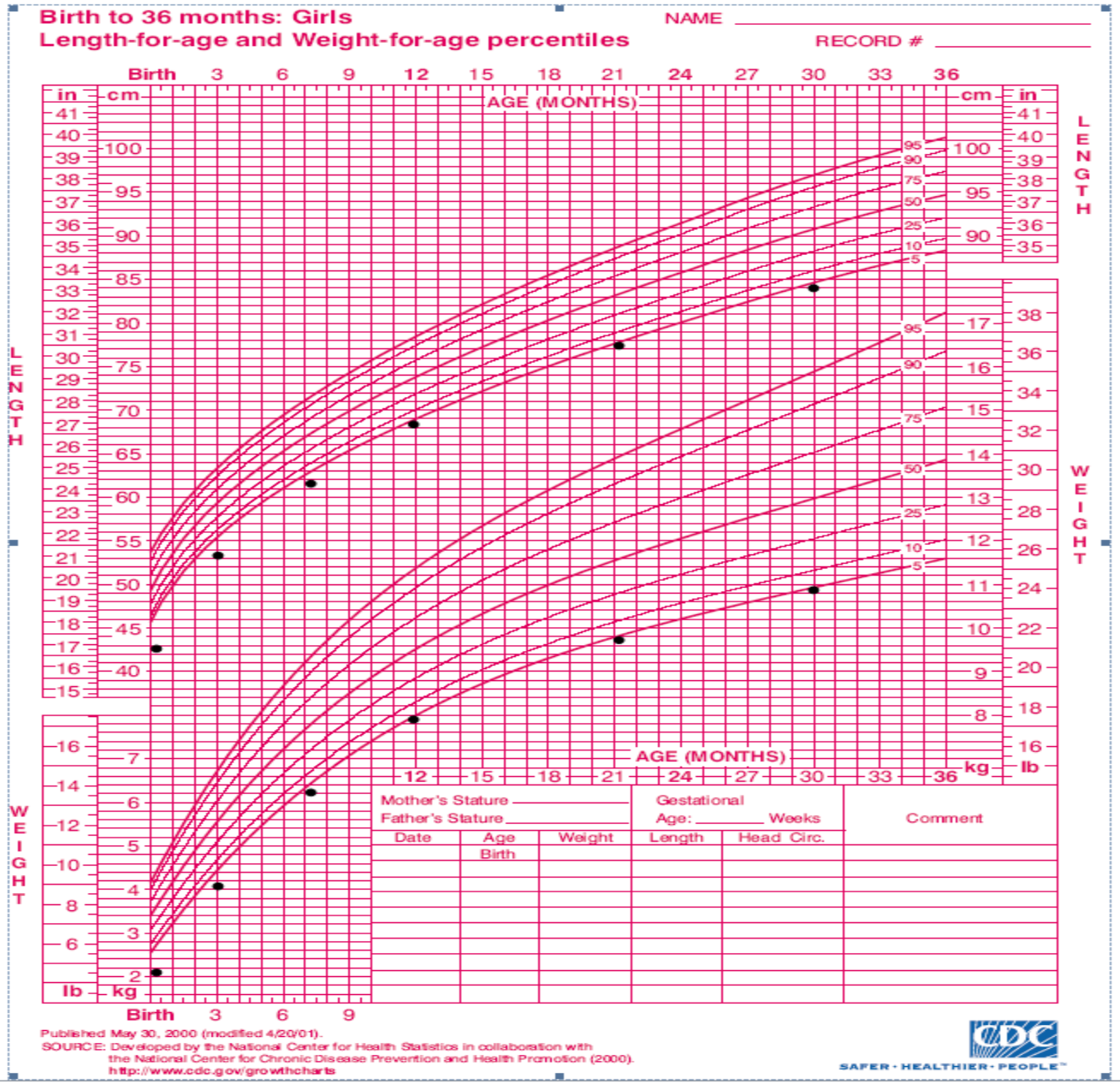
- Intracranial hypertension (pseudotumor cerebri)
- Edema
- Slipped Capital femoral epiphysis
- Worsening of scoliosis
- Hyperglycemia

Wilson et al. *J Pediatr.* 43: 415-21, 2003

Case # 5

- This is your first visit with Tina E. Small.
- She is a 30 month old girl who was referred for evaluation of short stature.
- She was born at 34 weeks gestation with a weight of 2100 grams and length of 43 cm.
- Mother is 5'1" and father is 5'5".

Case 5



Premature infant with catch up growth
Marked acceleration of height and weight in the first 3-6 months, then paralleling the normal growth curve.
Normal weight for length, normal BMI
Normal growth velocity
Normal bone age

Small for Gestational Age

- SGA defined as having birth weight and/or length less than 2 standard deviations below the mean given their gestational age and sex (below 3%)
- Majority of these children experience a normal growth pattern

- 10% to 20% fail to show linear catch-up growth by 2 to 3 years of age[1]

- Mean final adult height in SGA babies is reduced by 3-4 cm compared to mid parental height.

- Endocrine disorders associated with being born SGA
  - Premature adrenarche
  - Insulin resistance
  - Ovarian hyperandrogenism
  - Reduced pubertal growth
- Adults born SGA have increased risk for[2]
  - Type 2 diabetes mellitus
  - Hypertension
  - Cardiovascular disease

Kappy et al.*PediatricPractice Endocrinology*,McGraw Hill, 2010[1]
Stroescu R. Obes Res Clin Pract. 2014[2]

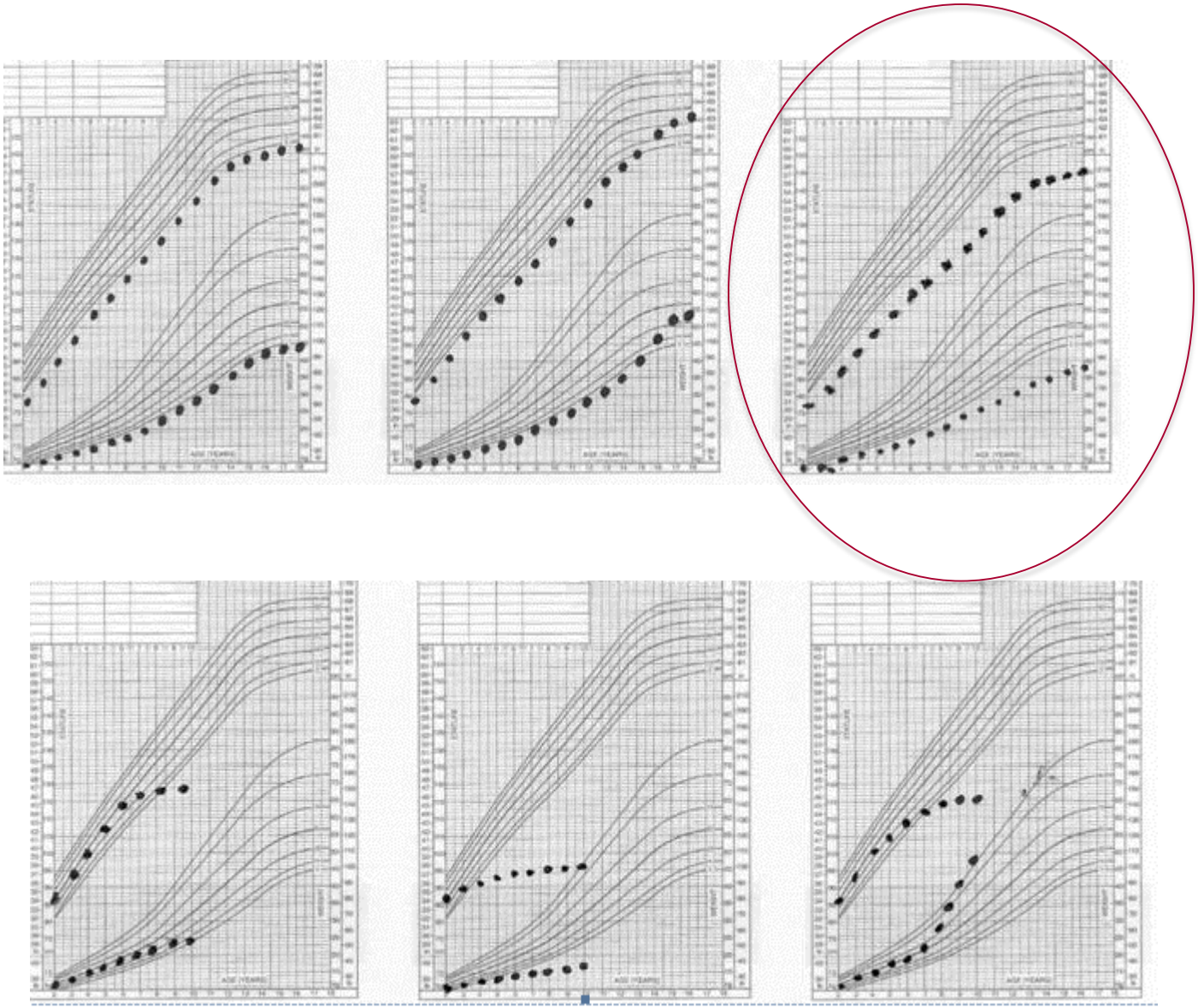
Case # 6

- Tracy M is 8 years old and comes with her mother, who wanted to find out why she is not growing like her peers. She seemed to grow normally until age 2 but later it became obvious that she was falling behind. She reports no complaints. The family moved to California 6 months ago. Based on what you have learned, you remember the importance of assessing the height and weight over time, so you request her previous records. In the meantime, you consider several possibilities:

What is your differential diagnosis?

- Genetic short stature
- Constitutional growth delay
- Turner's syndrome
- Hypothyroidism
- Growth Hormone deficiency
- Cushing's syndrome

Which growth chart typical for Turner Syndrome?



Turner Syndrome

- Common chromosomal disorder
- Affects approximately 1 in 2000 females[1]
- short stature and ovarian dysgenesis in females two main characteristics[2]
- Many organ systems can be affected
- Single X chromosome and absence of all or part of the second sex chromosome
- Majority (99%) of these spontaneously abort usually during first trimester of pregnancy[3]

Saenger et al. *JCEM* 86: 3061-3069,2001[1]
Davenport. *JCEM* 95: 1487-1495,2010[2]
Bondy. *JCEM*. 92: 10-25, 2007[3]

TABLE 1. Clinical features of TS by frequency and etiology

	Haploinsufficiency of genes on the X chromosome				
	SHOX		Putative	Germ cell survival	
Frequency	Physical	Medical	lymphatic gene	genes	Other/unknown
Greater than 50%	Short stature Prominent ears Retrognathia Narrow palate	Growth failure Chronic otitis media Low BMD Fractures	Low posterior hairline Lymphedema Nail dysplasia	Infertility Gonadal failure Delayed puberty	Learning disability Unfavorable body composition
25–50%	Cubitus valgus Short fourth metacarpals Ptosis[a] Strabismus[a]	Feeding problem Sensorineural hearing loss[a]	Webbed neck		Renal malformation Hypertension Multiple nevi
10–25%	Epicanthal folds[a] Scoliosis Kyphosis Pectus excavatum Flat feet	Obstructive sleep apnea Articulation problems	Single palmar crease Inverted nipples[a]		Hypothyroidism Aortic coarctation Bicuspid aortic valve Increased liver enzymes Diabetes mellitus
Less than 10%	Genu valgum Madelung deformity Patellar dislocation	Hyperacusis			Celiac disease Inflammatory bowel disease von Willebrand's disease JRA Pilomatrixoma Aortic dissection Prolonged QT

JRA, Juvenile rheumatoid arthritis.

[a] Relationship to haploinsufficiency not well established.

Davenport. *JCEM* 95: 1487-1495,2010

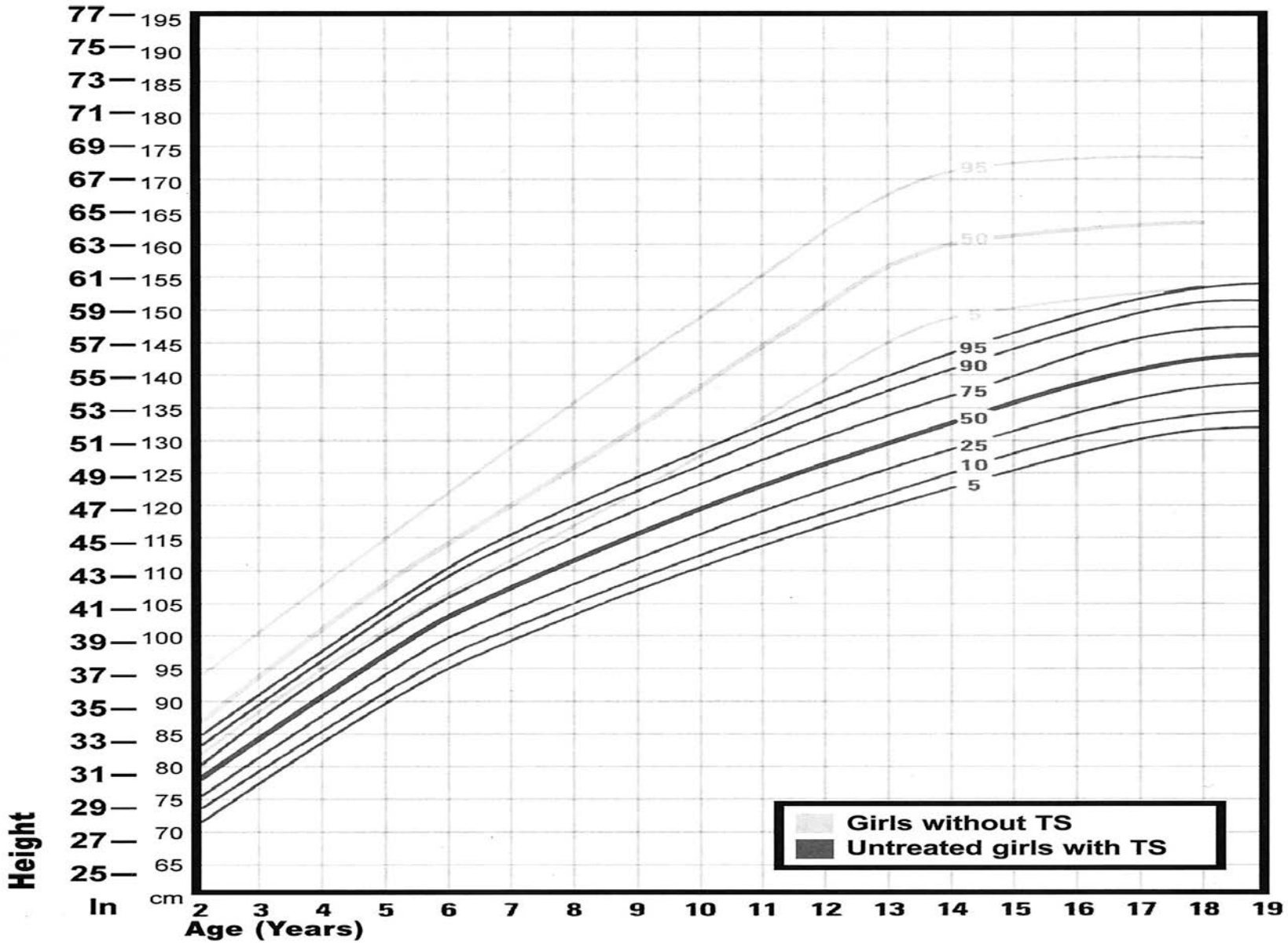
TABLE 2. Health care checklist for individuals with TS[a]

Problems	Screening test/referral	Timing of Tests: At Dx	Q visit	Q year	Other
Hip dislocation	Physical examination (including height, weight, BP, and calculation of BMI)	X	In infancy		
Feeding problems		X	In Infancy		
Strabismus		X	4 months to 5 yr		
Otitis media		X	All childhood		
Growth failure		X	All childhood		
Pubertal delay		X	Adolescence		
Scoliosis/kyphosis		X	While growing		
Dysplastic nevi		X	School-age on		
Lymphedema		X	Lifelong		
Hypertension		X	Lifelong		
Needs information/support	Refer to TSS, other support groups	X			
Structural renal abnormalities	Renal ultrasound	X			
Cardiac abnormality[b]	Examination by cardiologist; EKG; MRI/echo	X			Q 5–10 yr
Conductive and SNHL	Formal audiology exam	X			Q 1–3 yr
Gonadal dysfunction	FSH, LH	X			At ages 0.5–3 and 10–12 yr
Strabismus and hyperopia	Formal eye examination	X			At 1–1.5 yr
Celiac disease	Serum IgA, TTG IgA Ab	X			Q 2–5 yr (begin about age 4 yr)
Autoimmune thyroid disease	T_4, TSH	X		Begin about age 4 yr	
Developmental, educational, social problems	Developmental, educational, and/or psychosocial examination	X			Before school entry
Palatal/occlusive abnormalities	Orthodontic evaluation				At age 7 yr
Sexuality; school and/or work plans	Counseling			Begin about age 10 yr	
Renal and liver dysfunction	Cr, BUN, LFTs, CBC	X		Begin about age 15 yr	
Metabolic dysfunction	Fasting BG and lipids			Begin about age 15 yr	
Low BMD	DEXA scan				At about age 18 yr
GH action	IGF-I/IGFBP-3			During GH tx	

BG, Blood glucose; BUN, blood urea nitrogen; CBC, complete blood count; cr, creatinine; Dx, diagnosis; DEXA, dual-energy x-ray absorptiometry; echo, echocardiogram; EKG, electrocardiogram; IGFBP-3, IGF binding protein-3; LFT, liver function test; SNHL, sensorineural hearing loss; TTG IgA Ab, tissue transglutaminase IgA antibodies; Q, every; tx, treatment.

[a] These guidelines were adapted from Davenport and Calikoglu (40) and Bondy (a guideline of the Turner Syndrome Study Group) (10) and reflect the author's clinical practice. They suggest minimal routine screening evaluations. If the patient has a problem in one or more areas, she will generally be followed up by a specialist in those areas and evaluated more frequently.

Davenport. *JCEM* 95: 1487-1495,2010



Frias et al. *Pediatrics*. 2003 Mar;111(3):692-702

Turner Syndrome and Growth Hormone

- Growth failure problems for virtually all individuals with Turner Syndrome[1]
- Untreated individuals achieve an average adult stature 20 cm shorter than peers[1]
- Growth failure begins in utero, continues infancy and childhood
- Absence of pubertal growth spurt[2]
- Growth hormone therapy is standard of care
- Randomized control trial in which girls treated with growth hormone for mean 5.7 years averaged 7.2 cm taller than those in the control group[3]

Davenport, JCEM 92:3406-3416,2007[1]
Davenport, JCEM 95: 1485-1495,2010[2]
Stephure et al. JCEM 90:3360-3366,2005[3]

TABLE 3. Pubertal induction and maintenance estrogen therapy using TDE: a protocol using low growth-promoting doses for 18–24 months[a]

Treatment (months)	Target E2 (pg/ml)[b]	E2 dose	Notes
			Consider initiation of puberty at age 11–12 yr if there is no breast development.
0	3–4	0.1 μg/kg	Cut and apply a portion of a matrix patch to deliver 0.1 μg/kg E2. Apply in p.m. and remove in a.m.[c]
6	3–4	0.1 μg/kg	Wear a 0.1 μg/kg equivalent portion of the patch continuously. Change patch as directed (once or twice weekly). Check random E2 level to ensure E2 is in target range.
12	6–8	0.2 μg/kg	
18	~12	12.5 μg	E2 levels below this are believed to accelerate growth more than bone maturation.
24	~25	25 μg	
30	~37	37.5 μg	
36	~50	50 μg	Start progestin (earlier, if breakthrough bleeding occurs): 200–300 mg micronized oral progesterone for about 12 d/month qhs (causes drowsiness) or 5 mg oral medroxyprogesterone for about 12 d/month.
42	~75	75 μg	
48	50–150	100 μg	Typical adult dose; may not be high enough to protect liver, arteries, *etc*.

E2, 17β-Estradiol; qhs, before bedtime.

[a] This protocol is but one of many that can be used. This specific protocol is used in the author's clinic and individualized, depending on patient circumstances and desires. For example, older girls may want to be started at 25 μg.

[b] To convert picograms per milliliter to picomoles per liter, multiply by 3.671. E2 levels should be monitored using liquid chromatography/tandem mass spectroscopy technology.

[c] Vivelle Dot, matrix transdermal patch, is small and tends to adhere well. One-sixth to one-eighth of a 25 μg patch is approximately 0.1 μg/kg dose.

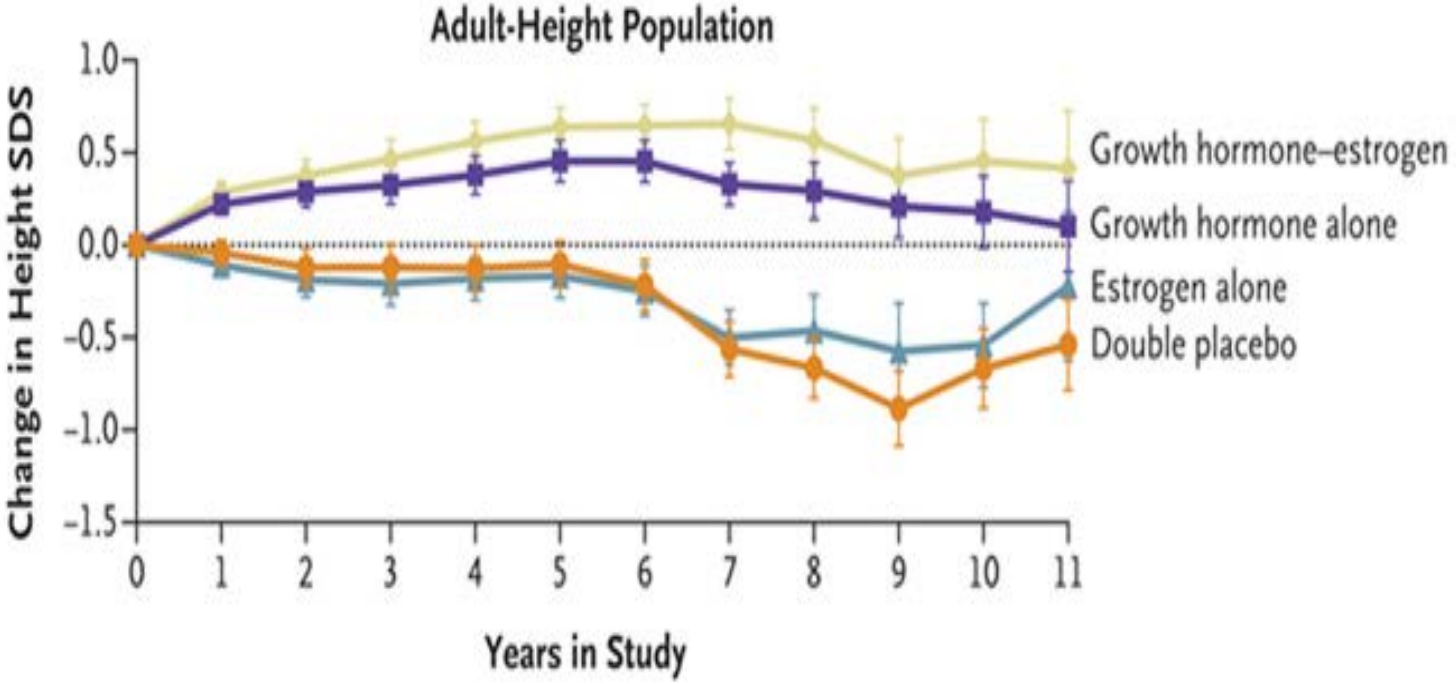
Davenport ML**Approach to the patient with Turner syndrome.** J Clin Endocrinol Metab. 2010,

Growth Hormone plus Childhood Low-Dose Estrogen in Turner's Syndrome

- Double –Blind Placebo Controlled trial 1987 to 2003 (enrollment closed 1996)
- 149 girls
- 5 years to 12.5 years of age
- Four groups
  - Double placebo
  - Estrogen alone
  - Growth hormone-estrogen group
  - Growth hormone-alone group
- Dose of Ethinyl Estradiol:
  - 25 ng/kg/day children 5 to 8 years
  - 50 ng/kg/day 8 to 12 years age
- At first visit after age 12 years patients received escalating doses of ethinyl estradiol
- Adult height was greater in growth hormone-estrogen group than in growth hormone alone group
  - 0.32 ± 0.17 standard deviation score (2.1 cm) (P=0.059)
- Modest synergy between childhood low-dose estradiol and growth hormone

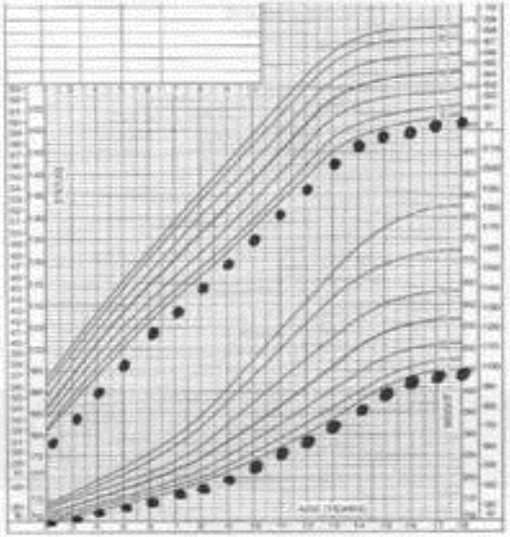
Ross et al. *N Engl J Med*. 364(13): 1230–1242,2011

B

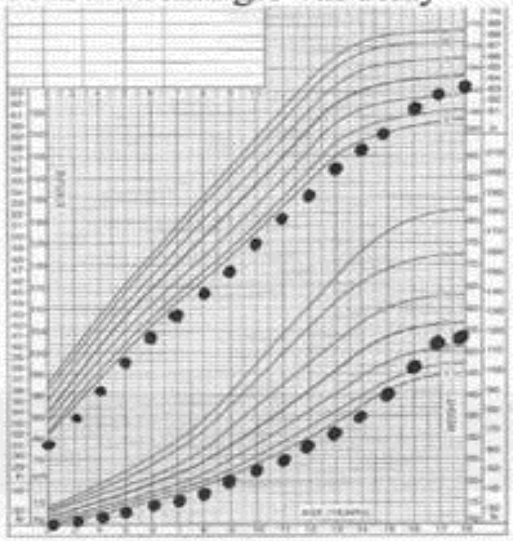


No. of Patients												
Growth hormone–estrogen	25	25	25	25	25	25	22	15	12	9	7	4
Growth hormone alone	27	27	26	26	25	22	23	22	16	14	12	9
Estrogen alone	21	22	22	22	22	21	17	15	11	7	8	3
Double placebo	17	17	17	16	16	16	14	12	13	9	8	7

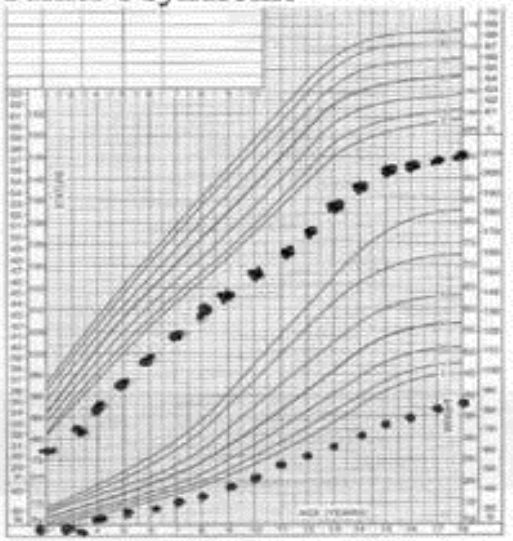
Genetic short stature



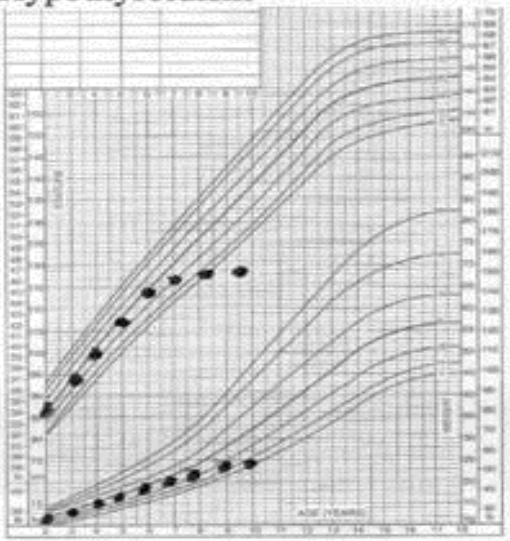
Constitutional growth delay



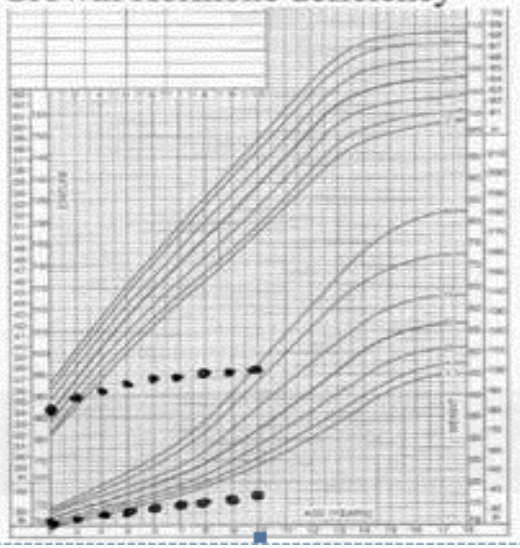
Turner's syndrome



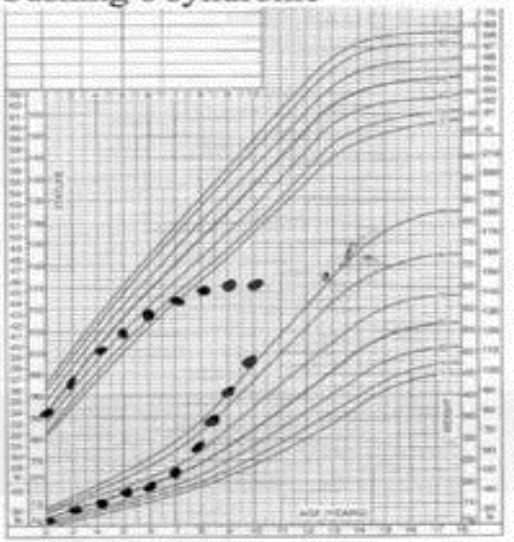
Hypothyroidism



Growth Hormone deficiency



Cushing's syndrome



Summary

- The clinical significance of the short stature depends on several factors:
  - genetic potential
  - growth velocity
- The two most common causes of short stature
  - familial short stature
  - constitutional delay of growth
- An estimate of a child's adult height potential can be obtained by the midparental height
- The history and physical examination should include
  - family history of growth and pubertal onset
  - Review of systems for features suggestive of gastrointestinal, pulmonary, immunologic, or other systemic disease
- Children with short stature and normal growth consider evaluation with bone age
- Children with severe short stature (eg, height ≤-2.5 SD [0.6th percentile]) or growth failure should be further evaluated