SHORT STATURE
History

- Rawan s a 13 y old girl , student in 7th grade, admitted through OPD in April 16, 2005.
- **CC: short stature**
- 1st noted to be short at age 5y, no growth deceleration, normal weight.
- Product FTNVD BW 2.7, LT 47cm, HC 35cm.
History

- No h/o chronic diarrhea, abdominal pain, vomiting, jaundice
- No h/o cough, wheezing, sob, BA, steroid use, recurrent chest infections
- No h/o cyanosis, chest pain palpitations, edema
- No h/o recurrent UTI, polyuria, oliguria.
- NO h/o visual disturbances, seizure, motor weakness
- No h/o hematological disease
- No h/o suggestive of thyroid disease
- Normal development, average school performance
History

Family history:

- Mother menarche 13 y, father growth spurt?
- Short stature in distant paternal cousins on GH therapy
- Delayed puberty in paternal uncles
Examination

- Pt well looking, not P J or C, with narrow forehead, small face, obese, no dismorphisms
- puberty Tanner stage II breast & pubic hair

Growth parameters:
- Ht 126cm < 5th% height, age 71/2 y, SDS = -3.7
- MPH 153+8.5
- U/L 0.9
- Wt 47Kg 50-75, BMI 28%
- HC 51 cm

Normal systemic examination
Differential diagnosis

- Turner Syndrome
- Systemic illness
- Familial short stature
- Constitutional short stature
- GH deficiency (isolated /combined)
Investigations:

- CBC, RFT, LFT, UA
- Chromosomal analysis
- TFT
- Bone age delayed 9y /6m

- GH provocation test:
  *Clonidine:
  GH 0.12, 0.15, 0.21, 0.19, 0.32, 0.11 <10ng/ml
  *Insulin:
  GH 0.15, 0.11, 0.09, 0.07, 0.15, 0.2, 0.16, 0.10, 0.17 <10ng/ml
Diagnosis:

GH deficiency

Management

- Pituitary MRI
- Start GH 0.3mg/kg/wk daily doses
SHORT STATURE
Normal Growth Physiology

- **Growth** is the natural increase in body size, as well as size of different organs, achieved by cell multiplication & increase IC substances.

- Growth is the multi factorial continuous process.

- The most fundamental feature of childhood is that it is a period of growth.
Phases Of Human Growth

**Prenatal:**

- **Influenced by**
  - nutrition, genetics, maternal factors, placental factors, intrauterine infection, endocrine factors (IGF2).
  - The fastest growth rate.
  - birth size predominantly relating to maternal factors rather than fetal factors.
Post natal growth: 3 phases

- Infancy: nutrition
  22 cm/y
- Childhood: thyroxin, GH
  5-7 cm/y
- Puberty: GH, sex hormones
  10-12 cm/year
Assessment of growth

- <2y supine Lt
- >2y standing Ht (stediometer)
- Sitting Lt
- UL
- Arm span
- Weight, HC
- BMI, mid arm circumference & skin fold thickness
- Pubertal stage
- MPH: father + mother / 2 + 6.5
Growth Charts

- Series of percentile curves that illustrate the distribution of skeletal body measurements based on cross sectional population studies.
Short stature

**Definition:**
- Ht > 2 SD below expected mean for age
- Ht velocity < 3rd percentile or <4 cm at any age.
- By definition 2.5% of the population is short. However, the number of children with poor linear growth is higher given the frequency of chronic diseases of childhood
- short boys are more likely to come to medical attention than short girls.
Causes

1) Normal variants  - genetic (familial )  
   - constitutional

2) Abnormalities intrinsic to growth plate  
   - skeletal dysplasia  
   - Chromosomal anomalies  
   - IU growth retardation

3) 2yr short stature  
   - malnutrition  
   - systemic illness  
   - Endocrine causes
Normal Variants

**Familial Short Stature**
- Ht < 2.5 SD
- Ht within MPH
- NL Ht velocity
- Bone age = chronological age
- 2 subtypes
  - NL puberty
  - delayed puberty
Normal Variants

- **Constitutional growth delay:**
  - No systemic illness, NL nutrition, NL physical examination.
  - Growth deceleration 18-30 m, steady growth velocity
  - Ht <2 SD  Ht < MPH
  - Bone age < chronological age
  - Normal Adult Ht
  - Delayed puberty
Primary Growth plate
Abnormality
Osteochondrodysplasia

- Heterogenous group with intrinsic abnormality in cartilage & bone
- Characterized by genetic transmission, abnormality in size & shape of bones, radiological abnormality of bone.
- AD+ new mutation
- >100 types
- Achondroplasia is commonest 1/26000
- FGFR3 on Ch 4, AD, 90% new mutation
II. Chromosomal anomalies

- Cause of growth failure is unknown, does not affect GH or IGF

**Examples include:**
- Down Syndrome
- Turner syndrome (95-100% short, SHOX, mild IUGR, dec HT velocity 3-14 y, GH NL, GH therapy)

- Others: Ch 5 p deletion, Trisomy 13/18, Ch 18 q deletion
III-Intrauterine Growth Retardation

- IUGR = fetal BW & Lt <2 SD below mean GA
- Catch up growth 4y (15% fail), Low IGF1 IGFBP 3

**Etiology**

1. **Intrensic fetal abnormalities**
   - chromosomal disorders
   - syndromes with 1ry growth failure, (russel silver, seckel, noonan, progeria, cockyane, bloom, rubestiein taybi..)
   - IU infections

2. **Placental abnormalities** (abnormal implantaion, vascular insufficiency..)

3. **Maternal factors** (malneutrition, smoking, drugs, uterine malformations, PET...)

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Secondary Growth Disorders
I-Malnutrition

- Commonest cause of growth failure worldwide
- Increase in GH & stimulated GH in kwashiorkor)
- Adaptive process spare protein due to lipolytic & anti insulin effect of GH
- NL GH in marasmus
II-Chronic Illness

- GI
- CV
- Renal
- Hematological
- Pulmonary
- Chronic infections
- Inborn error of metabolism
- Immunodeficiency
- DM
Endocrine Causes

Account for 5% of causes for short stature:

- Hypothyroidism
- Cushing syndrome
- Pseudo-hypoparathyroidism
- GH deficiency
GH deficiency:

- hypothalamic dysfunction
- Pituitary GH deficiency
- GH insensitivity
Hypothalamic Dysfunction

a. Congenital malformation of hypothalamus (holoprosencephaly, septo-optic dysplasia)
b. Molecular defect of GHRH or GHRH receptor
c. Trauma
d. Inflammation
e. Tumors
f. Irradiation
Pituitary GH deficiency

- Genetic abnormality-combined def : HESX, Reigs, PROP..
- Genetic abnormality in GH:
  - GHD IA, IB AR
  - GHD II AD
  - GHD III X linked
- Tumor, trauma, infection, irradiation
- GH neurosecretary dysfunction
- Bio-inactive GH
- Psychosocial dwarfism
GH insensitivity:

NL GH with failure to respond to exogenous GH
GHI + dysmorphism = Laron syndrome

1ry:
- GH receptor
- Post receptor abnormality
- IGF1 biosynthesis

2ry:
- Circulating Ab to GH
- Circulating Ab to GH receptor
- Illness
Clinical Features Of GHI

- NL BW & Lt & severe post natal growth failure
- Bone age delayed
- Miropenis
- Craniofacial: spares hair, frontal bossing small face, craniofacial disproportion, shallow orbit hypoplastic nasal bridge, delayed dentition, blue sclera, high pitched voice
- Metabolic: hypoglycemia, delayed motor mile stones, osteoporosis, infantile fat distribution
Diagnosis of IGF Deficiency

- GH secretion is pulsatile, surge in slow wave sleep (stage 3-4)
- Secretion varies with age, gender, physiological state, pubertal stage
- NL GH are low (< 1ng/ml)
  random GH level are useless in diagnosing GH deficiency
- Provocative test are indicated
- Neonate, random GH <20 ng/ml is diagnostic
Provocative test:

**Types:**
- **Physiological:** sleep, fasting, exercise
- **Pharmacological test:**
  *Screening:* clonidine, L-dopa
  *Definitive:* insulin, glucagon, arginine

Sub optimal response <10ng/ml
Neonate GH <20ng/m (random)

2 pharmacological tests needed for the diagnosis
Biochemical Evaluation of Growth failure

**Step I : defining the risk of GH deficiency:**

- Severe short stature SD < -3 Sd
- Severe growth deceleration Ht velocity <2 SD in 12m
- Ht <2 SD, HV <-1 SD over 12m
- Ht <1.5SD, HV <1.5 SD over 2y
- Risk factors: brain tumors, irradiation.

**If +ve** step 2

**If –ve** re-evaluate in 6 month
Step II: Scan for GH/IGF deficiency:
A: lab tests: bone age, TFT, chromosomal analysis
B: IGF1 & IGFBP3 > -1 SD review in 6m
     <-2 SD GH testing

Step III: Testing GH secretion
-2 stimulation tests if both low → step 4

*GH >15 - GHBP < -2SD IGF defect
     - GHBP NL follow in 6 month
*GH 10-15 back to step 2 in 6m
Step IV: Evaluate pituitary:
- MRI
- Test anterior pituitary hormones

Step V: Growth promotion:
- Initiate GH therapy
Treatment of GH deficiency:

- **Objective:**
  attain normal Ht in childhood & NL adult HT.

- **Therapy:**
  - rhGH (specie specific)
  - Dose 25-50mcg/kg/day
  - Accelerated effect in 1\textsuperscript{st} 3-4 y, then progressive weaning of the effect
  - Gain 10-12cm/y in 1\textsuperscript{st} y then 7-9cm/y in 2-3\textsuperscript{rd} y
  - Patient should be monitored at 3-6month intervals
Causes of Sub optimal response:

- Poor compliance
- In proper administration or preparation
- Chronic disease
- Glucocorticiod therapy
- Irradiation of spine
- Anti GH antibodies (10-20 %)
- Incorrect diagnosis
Side effect of GH therapy:
- Leukemia
- Pseudotumor cerebri
- Slipped capital femoral epiphysis
- Gynecomastia
- Scoliosis, kyphosis
- Neurofibromatosis
- Sleep apnea & behavior changes
- Abnormal glucose tolerance
- Hyperlipidemia
Evaluation Of Short Stature

**History:**
- length, weight, and head circumference at birth, relevant antenatal & postnatal event
- Assessing the heights of both parents is absolutely essential (MPH)
- Document pubertal timing in first-degree relatives. Determine the age at onset of menarche for the child's mother and the age of adult height attainment for the father.
History:

- **Review of symptoms by organ system**
  - **Gastrointestinal**
  - Diarrhea, flatulence, (suggest malabsorption).
  - Vomiting can suggest an eating disorder or a (CNS) disorder.
  - Dietary intake and composition. In particular, ask about intake of carbonated beverages, juices, and other casual intake.
  - Pain or abdominal discomfort suggests inflammatory bowel diseases.
Cardiac disease: peripheral edema, murmurs, and cyanosis.

Chronic infections: Poor wound healing and opportunistic infections are signs of potential immune deficiency.

Pulmonary
Sleep apnea can be a cause of short stature.
Other diseases that may result in short stature include severe asthma associated with chronic steroid use and cystic fibrosis.

Neurological
Visual field deficits often herald pituitary neoplasms.
Vomiting, early morning nausea, polyuria, or polydipsia often is associated with masses of the CNS.
- **Renal**
  - Polyuria and polydipsia
  - Chronic renal disease

- **Social**
  - Participation in sports requiring weight control, may uncover anorexia nervosa or bulimia induced by the patient, peers, or coaches.
  - Education, bullying, psychological impact
Physical Exam

- Measure standing height in triplicate using a calibrated wall-mounted stadiometer.
- For children who cannot stand or recline completely, arm span provides a reliable alternative for longitudinal assessment of long bone growth.
- Document growth velocity.
- Weigh all patients.
- In infants, determine the HC.
- Sitting height, U/L.
- Pubertal Assessment.
Thyroid enlargement
Test visual fields for signs of pituitary and/or hypothalamic tumors
Inspect fourth metacarpals, which are shortened in persons with pseudohypoparathyroidism-Turner syndrome, and Albright hereditary osteodystrophy.
Inspect mucous membranes for ulcerative stomatitis, typical of Crohn disease and various trace mineral and vitamin deficiencies.
Pretibial ulcerations observed in persons with IBD
Rectal tags and clubbing are also typical in individuals with Crohn disease
examine the midface.
A single, central, maxillary incisor reflects a defect in midline facial development.
bifid uvula, submandibular cleft palate,
Investigations

**Initial screen**
- Full blood count, ESR, BUN and electrolytes,
- bone profile, liver function tests
- thyroid function
- Urinalysis
- Skeletal (bone) age
- Karyotype (girls)
- antiendomyseal antibody
Specific investigations (when indicated)

- Endocrine ("provocation" tests)
- Gastrointestinal - for example, jejunal biopsy, antiendomyseal antibody
- Renal
- Respiratory
- Cardiac
- Radiological - for example, magnetic resonance imaging of the brain
Thank You