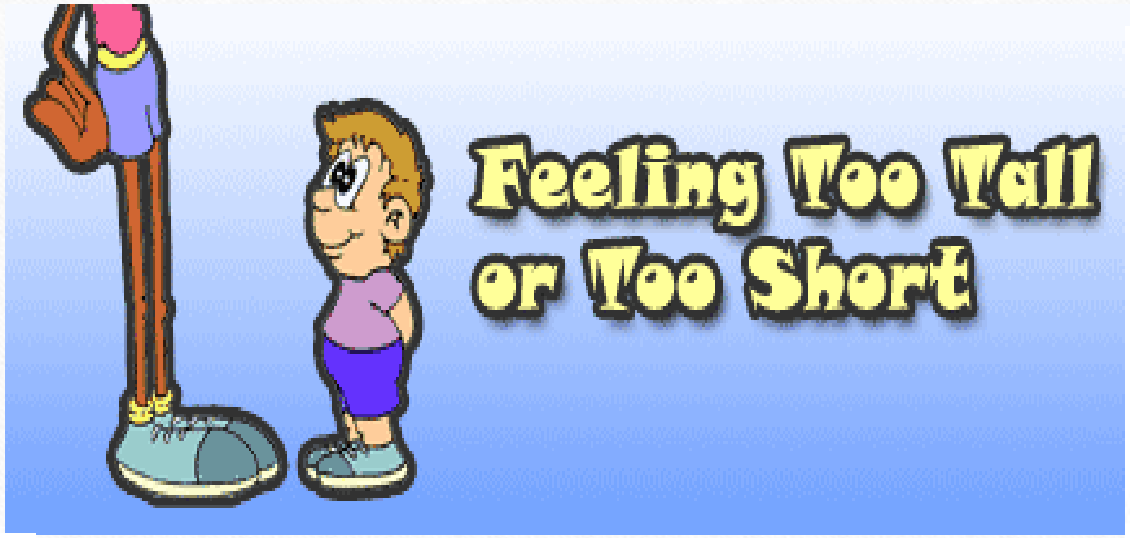
Child with growth disorders



Beata Pyrżak
Klinika Pediatrii i Endokrynologii
Warszawski Uniwersytet Medyczny

In the diagnostic approach – two important questions

(1) Which criteria should be used to refer children with impaired growth and to start diagnostic procedures?

(2) What kind of diagnostic approach should be followed in the referred group of children?

Referral Criteria for Children with Short Stature

1. Height can be compared with age references, and expressed as standard deviation score (SDS) or centile position. Height SDS (HSDS) is a measure of the deviation of the individual height from the mean, and is expressed as the number of standard deviations below or above the mean height of the population for the same age and sex.
2. HSDS can be compared with the sex-corrected midparental height (target height) SDS. E.g. formula (father's height + mother's height + 13 cm)/2 for boys and (father's height + mother's height - 13 cm)/2 for girls

Growth

The criteria most commonly used in clinical practice in short stature are:

(1) Height below–2 SDS for age, sex and ethnic group.
(2) Normal height, i.e. between ±2 SDS for the general population, but >2 SDS below the growth curve corresponding to the patient's TH (midparental target height)
(3) Projected adult height (prediction of adult height) >2 SDS below the TH.
(4) Persistent low GV.

Short stature can be definied as heigt more than 2 SD below the mean

Tall stature as height more than 2 SD above the mean.

Growth

- 3% of children will be or more than -2 SD below the mean (short stature)
- 3% of children will be or more than +2 SD above the mean (tall stature)

Growth hormone physiology

Two hypothalamic hormones regulate GH secretion:

Growth Hormone Releasing Hormone (GHRH) with a stimulatory action, and **somatostatin (SST)** with an inhibitory effect .

- Various synthetically produced GH releasing compounds and the recently discovered natural hormone **ghrelin** probably have a dual effect in increasing the release of GHRH and inhibiting SST action.
- **Stress, hypoglycaemia and ingestion of protein -high levels of circulating amino acids stimulates GH secretion**, while high levels of glucose and FFA inhibits secretion.

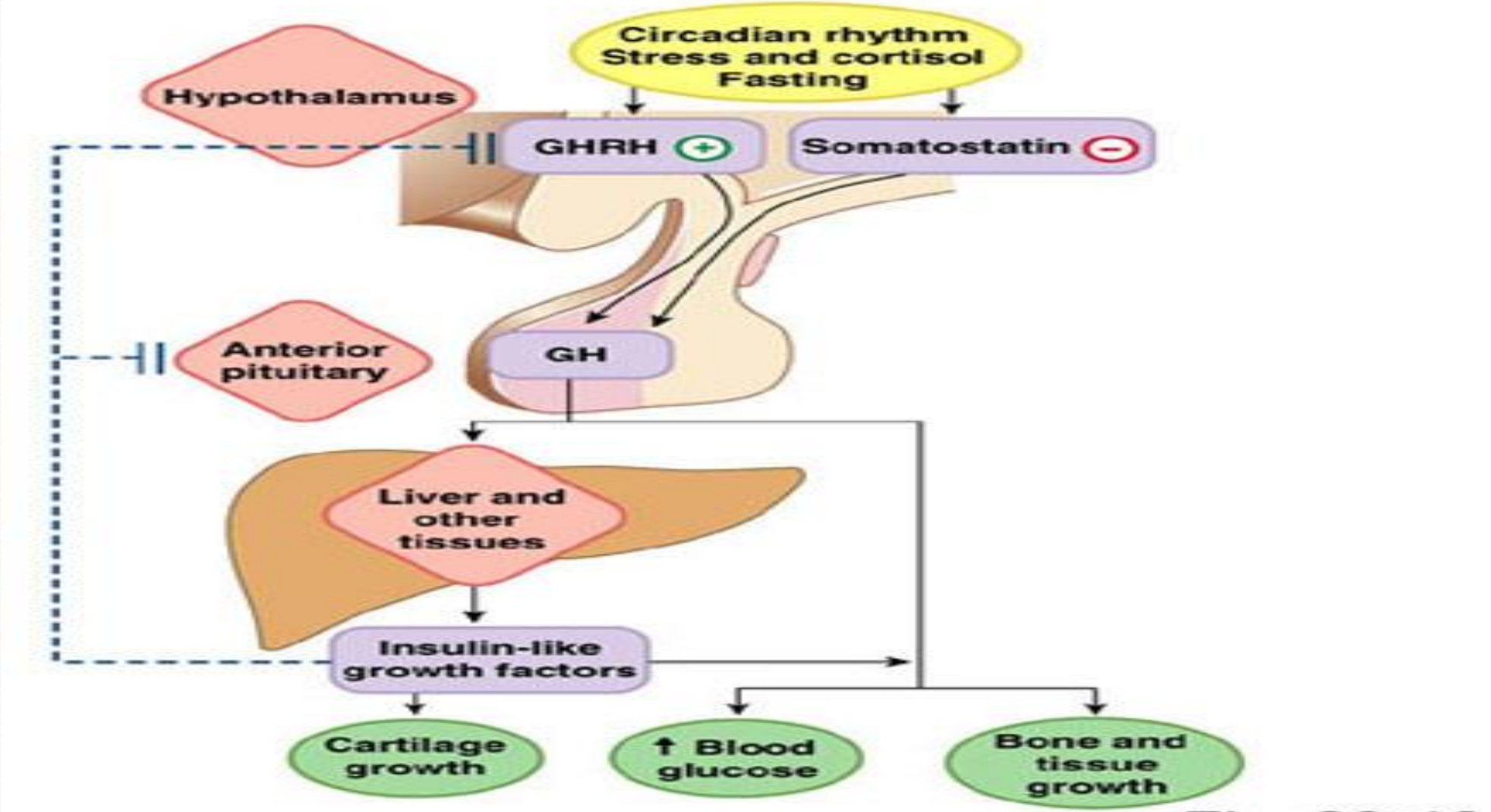
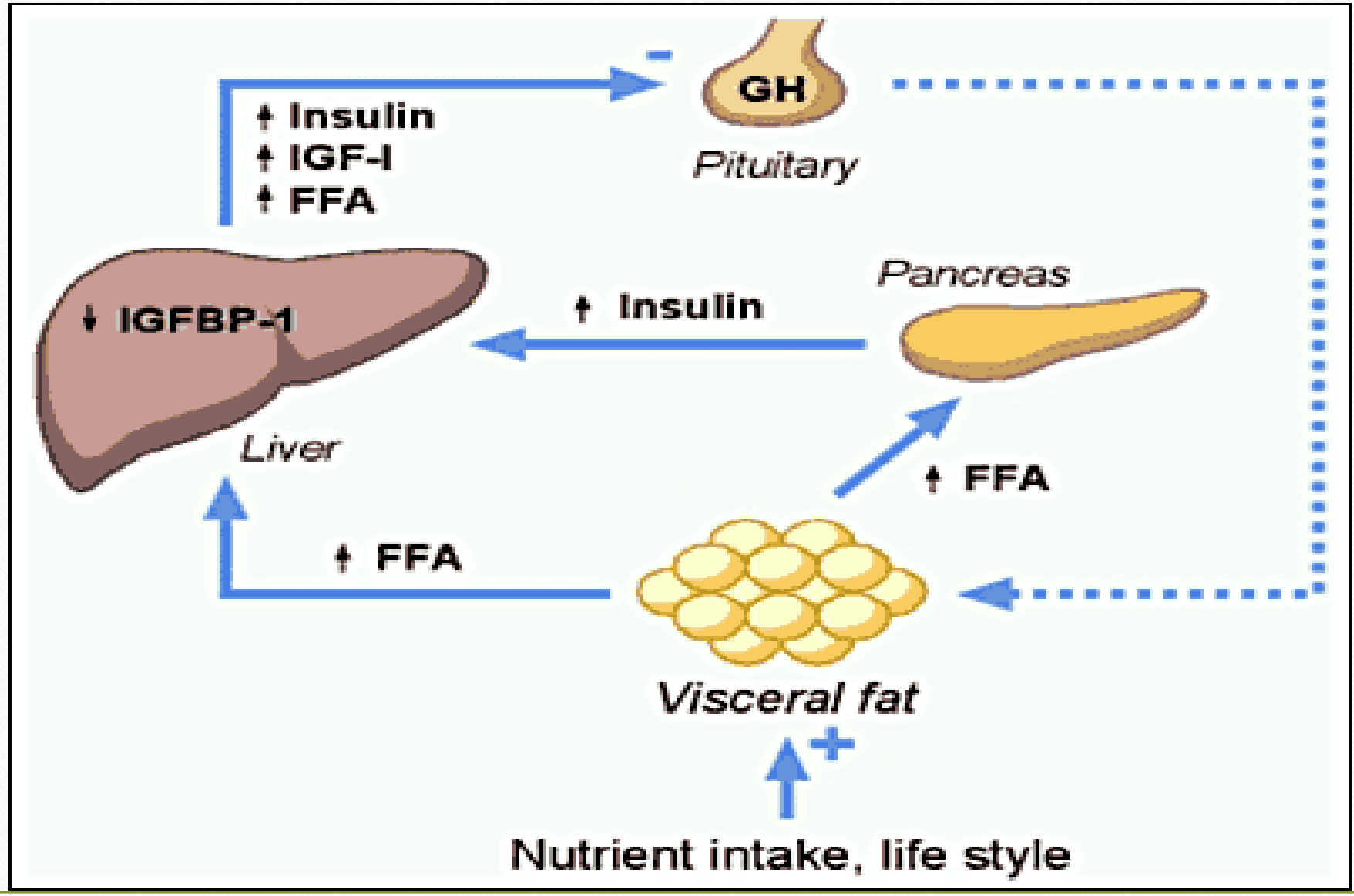


Fig. 23-16

Factors that stimulate and suppress GH secretion under physiological conditions



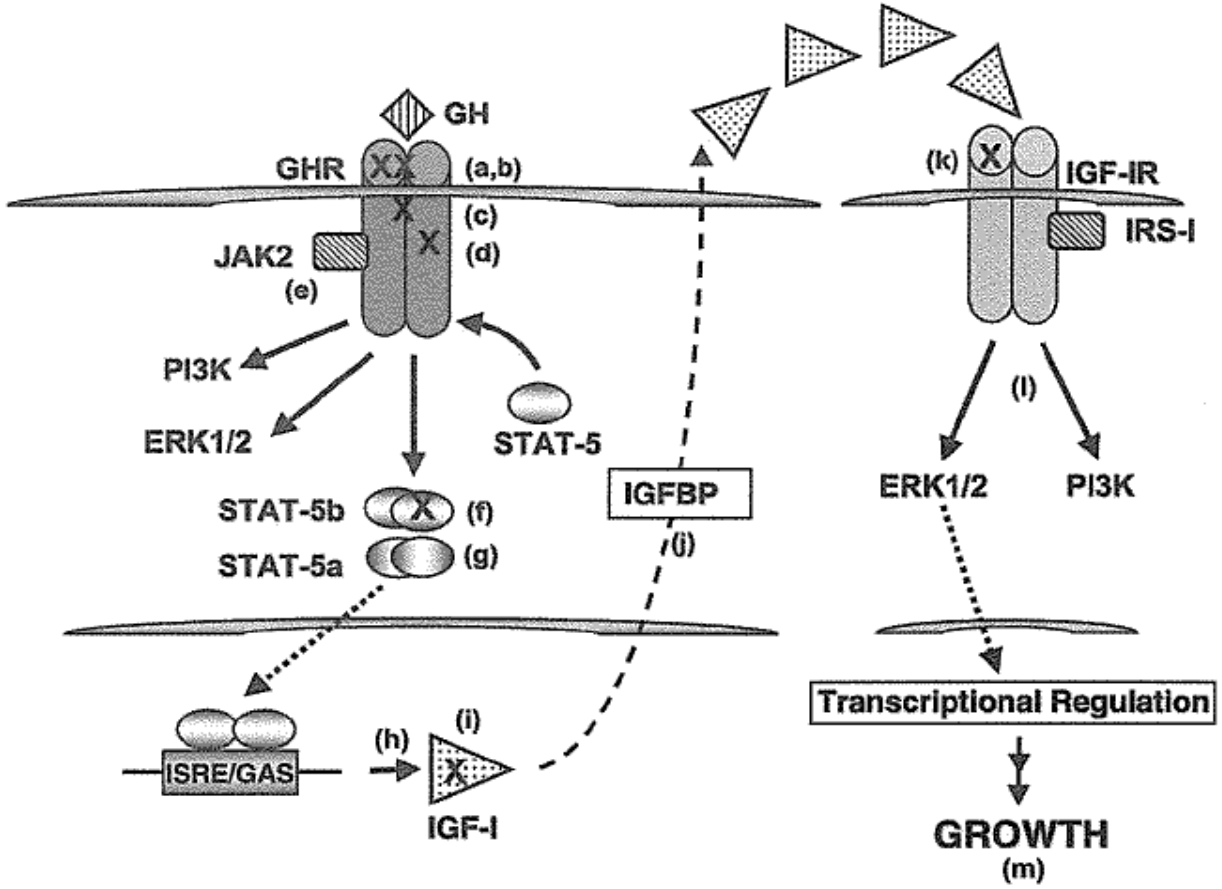


Figure 1 Schematic diagram of the GH–IGF axis, showing identified and theoretical defects: (a) defects of the extracellular domain of the GHR, affecting binding of GH; (b) defects in GHR dimerization; (c) defects of the transmembrane domain of the GHR; (d) defects of the intracellular domain of the GHR; (e) defects of JAK2 (theoretical at this time); (f) defects of STAT5b; (g) defects of STAT5a (theoretical at this time); (h) defects of transcriptional regulation of IGF-I (theoretical at this time); (i) defects of the IGF-I gene; (j) defects of IGFBPs, affecting IGF availability (theoretical at this time); (k) defects of the IGF receptor; (l) defects of IGF receptor signal transduction (theoretical at this time); (m) defects at the epiphyseal growth plate, potentially affecting IGF action. GH, growth hormone; GHR, growth hormone receptor; JAK2, janus-family tyrosine kinase 2; PI3K, phosphatidylinositol-3 kinase; ERK, extracellular signal-regulated kinase; STAT, signal transducer and activator of transcription; ISRE, interferon-stimulated response element; GAS, interferon-gamma-activated sequences; IGF, insulin-like growth factor; IGFBP, IGF binding proteins; IGF-IR, IGF-I receptor; IRS, insulin receptor substrate.

Effects on Growth

Growth is a very complex process, and requires the coordinated action of several hormones.

The major role of growth hormone

•in stimulating body growth is to stimulate the liver and other tissues to secrete IGF-I.

• stimulates proliferation of chondrocytes (cartilage cells), resulting in bone growth.

•Growth hormone have a direct effect on bone growth in stimulating differentiation of chondrocytes.

•IGF-I also appears to be the key player in muscle growth. It stimulates both the differentiation and proliferation of myoblasts. It also stimulates amino acid uptake and protein synthesis in muscle and other tissues.

Other functions

Although height growth is the best known effect of GH, it serves many other metabolic functions as well.

- It increases calcium retention, and strengthens and increases the mineralization of bone.
- It increases muscle mass through the creation of new muscle cells (which differs from hypertrophy)
- It promotes lipolysis, which results in the reduction of adipose tissue (body fat).
- It increases protein synthesis and stimulates the growth of all internal organs excluding the brain.
- It plays a role in fuel homeostasis.
- It reduces liver uptake of glucose, an effect that opposes that of insulin.
- It promotes liver gluconeogenesis.
- It contributes to the maintenance and function of pancreatic islets.
- It stimulates the immune system.

Growth phases

Human growth is a rather regular process characterized by a pattern of changing growth rate or height velocity from infancy to adulthood.

In the short-term the height velocity of a healthy individual fluctuates i.e. seasonal or longer periodicity has been shown.

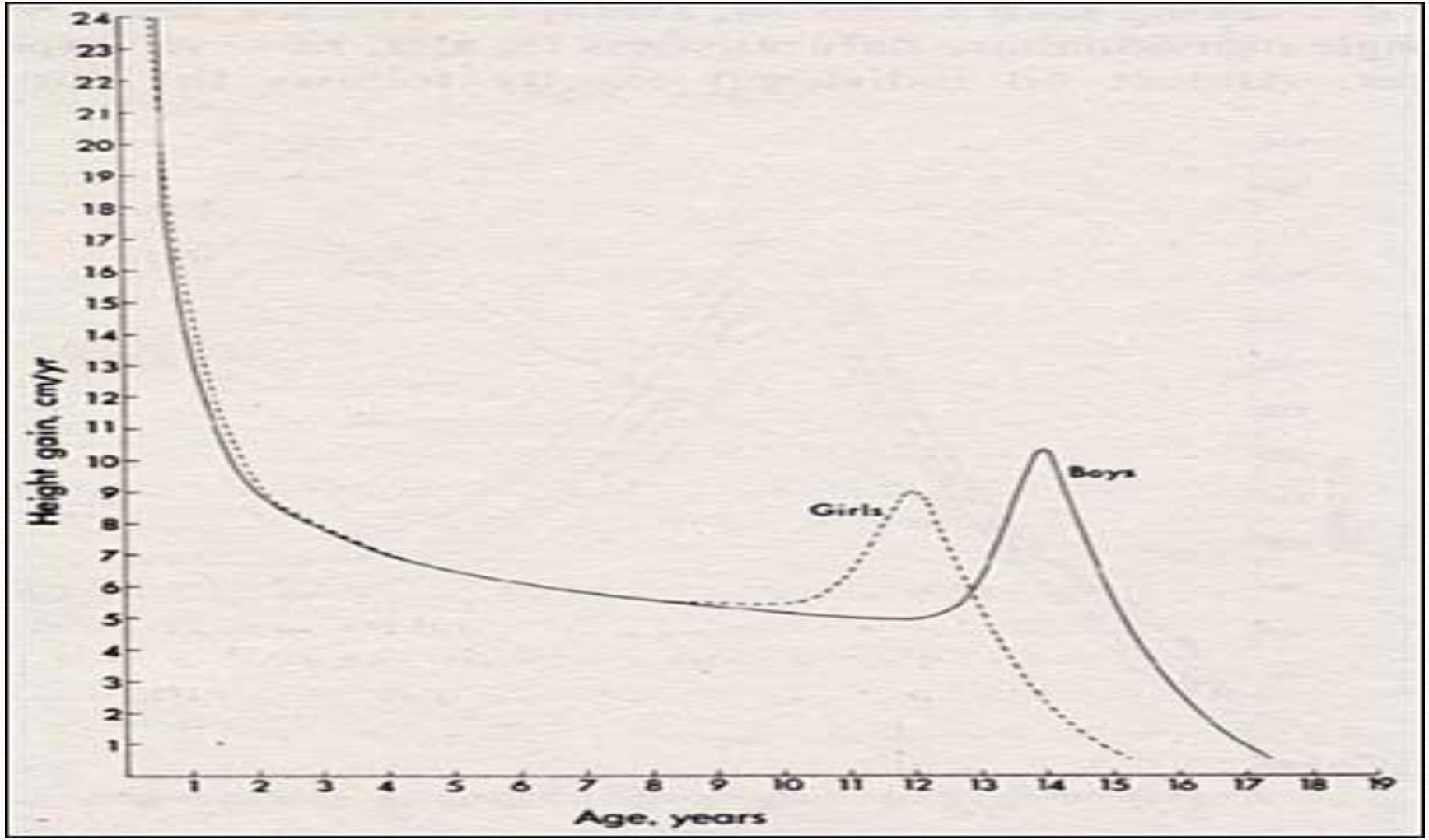
It appears that some phases of growth are more important in their effect on final height. For example a child who is born short has a greater chance of being a short adult. The timing and duration of puberty are also crucial factors in determining final height.

Growth velocity

- Height and weight at each age are the results of the genetic potential and the health history of the individual.
- **Growth velocity** /Height velocity – linear growth; observation of a child's height over a period of time -at least 6 months of observation/

Normal Growth velocities at different ages

Age	**Average Growth Velocity / Year.**
1st year	25cm
2nd year	12-13cm
3rd & 4th year	6-7 cm
5 years- till onset of puberty	5cm/year


Height gain, cm/yr
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Girls
Boys
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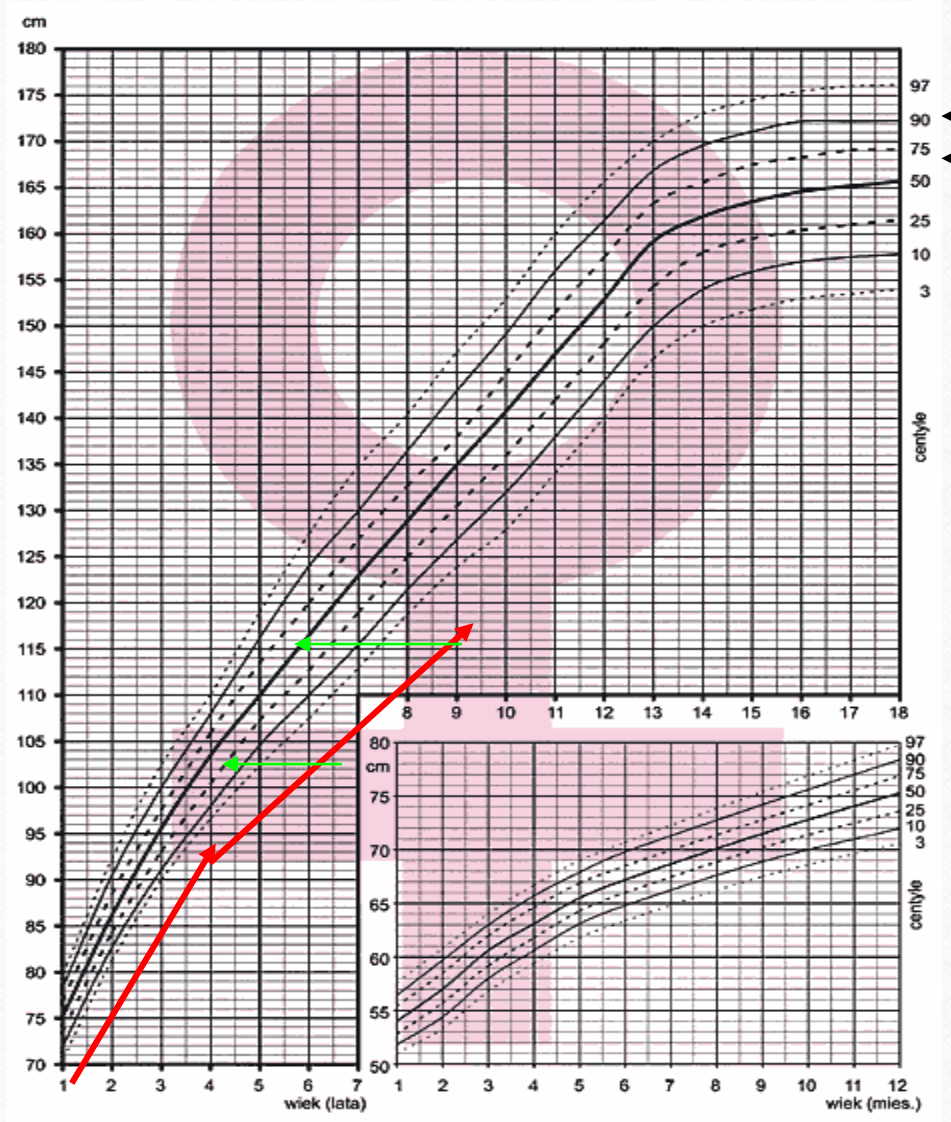
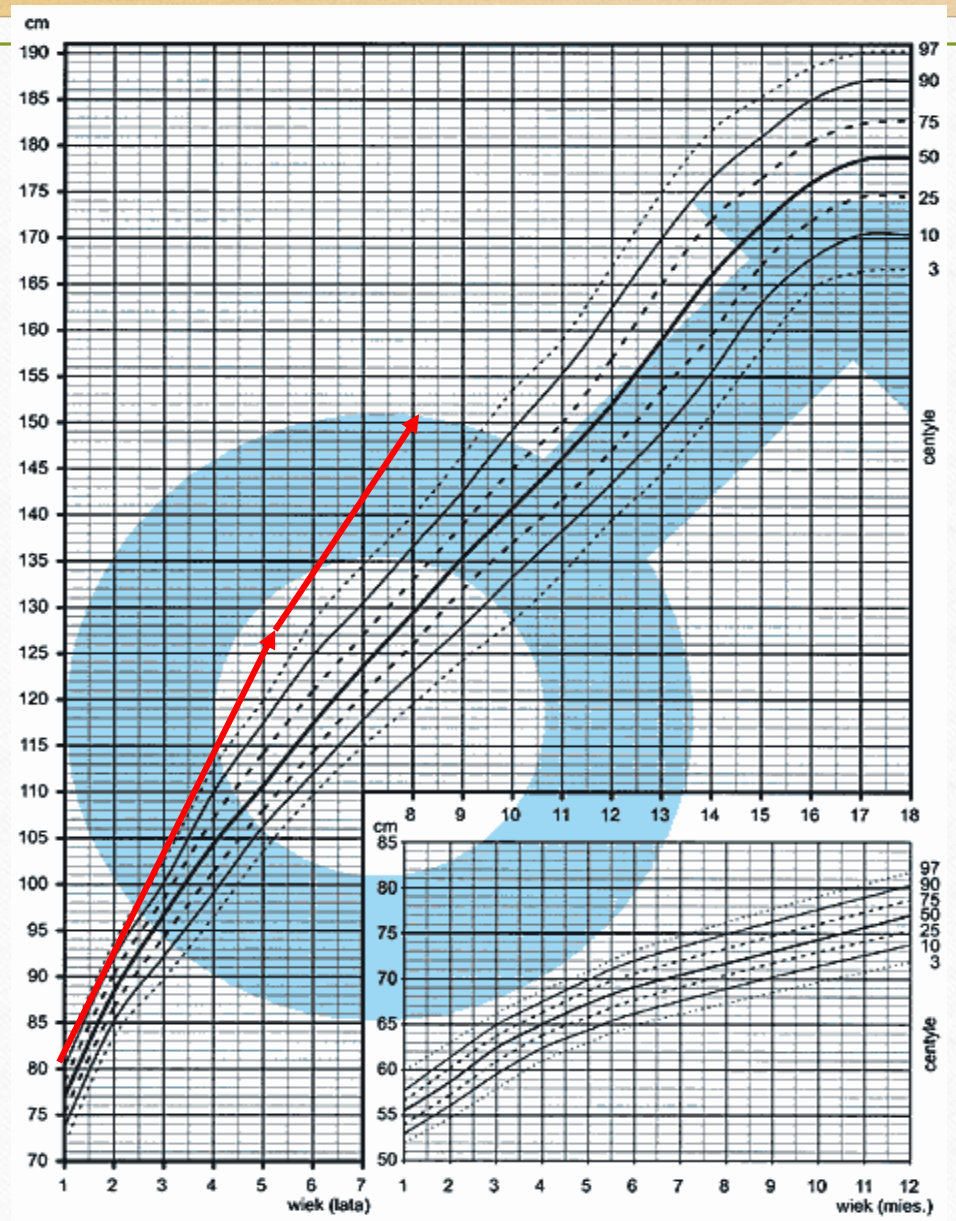
Age, years



← Father 187 cm
← Mother 166 cm

9 y.o girl with growth hormone deficiency
bone age delay at 6.y.o



← Father 182 cm

← Mother 160 cm

8 y.o boy with tall stature 151 cm /2 SD above the mean/

THE GROWTH PLATE

The most important target organ for linear growth is the epiphyseal growth plate, a layer of cartilage found in growing long bones between the epiphysis and the metaphysis. Longitudinal bone growth occurs at the growth plate by endochondral ossification, in which cartilage is formed and then remodeled into bone tissue

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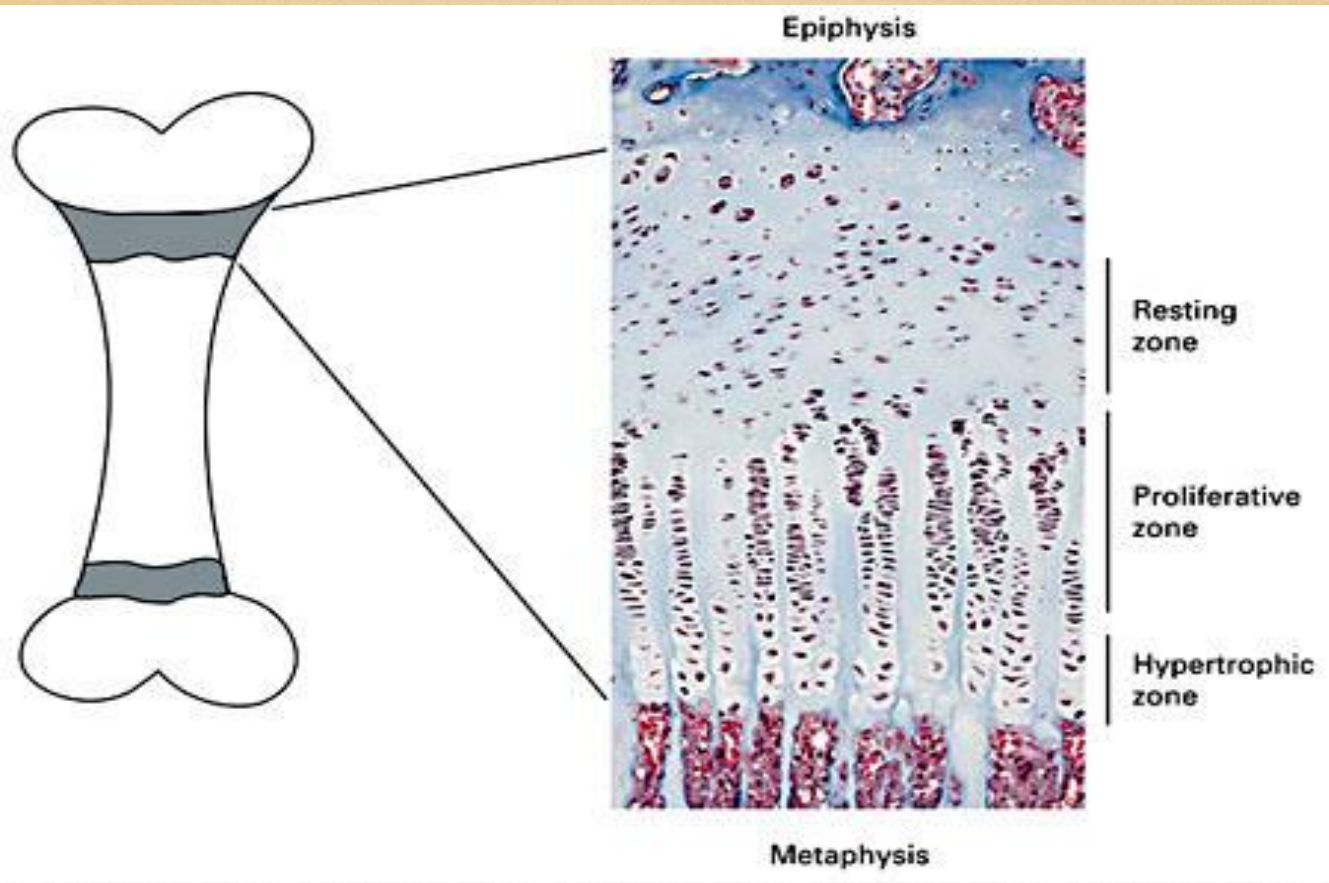


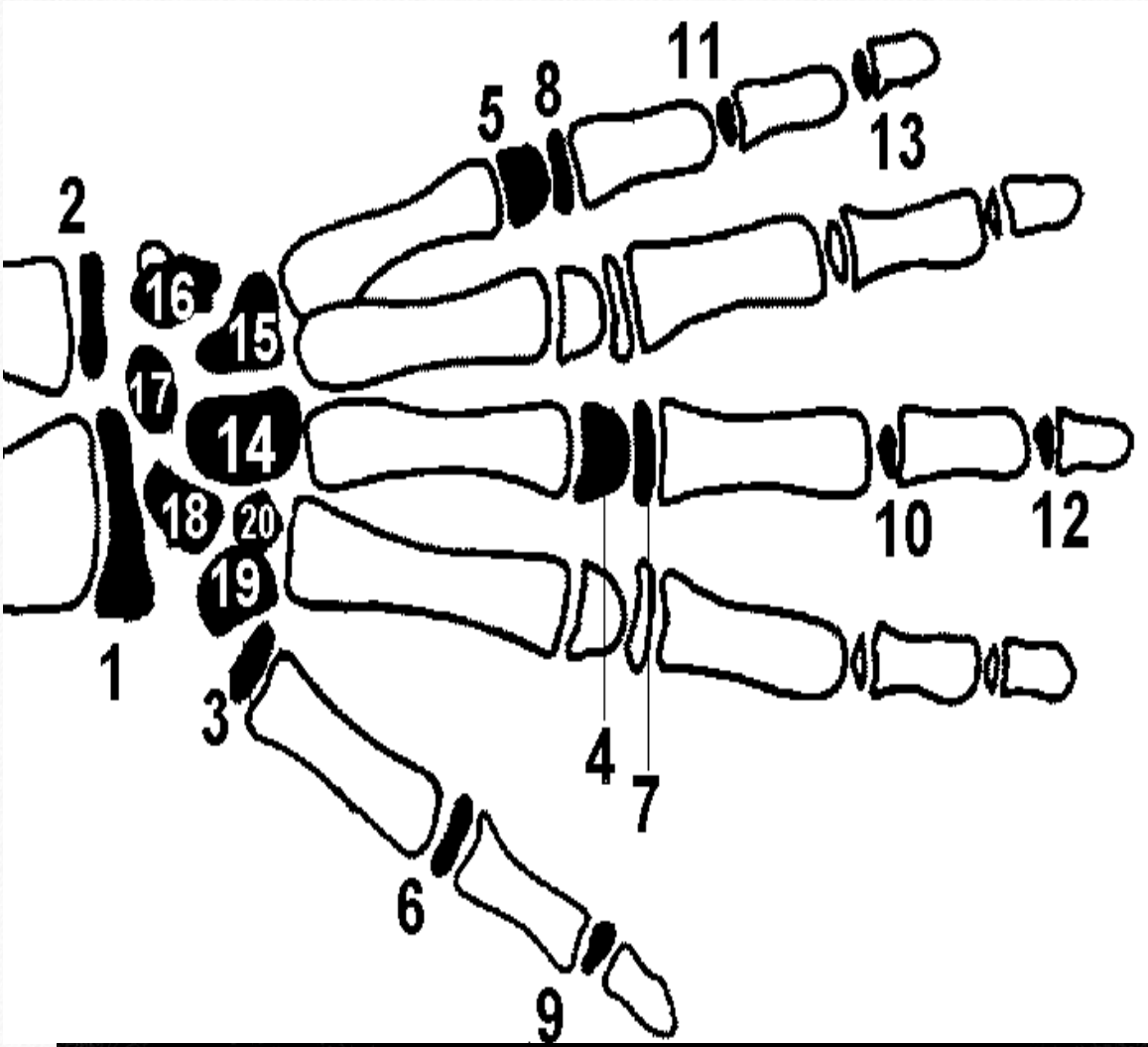
Fig. 1. Histology of the growth plate. The growth plate is a thin cartilage structure situated in the ends of tubular bones. It is commonly subdivided into three distinct zones; the resting, proliferative, and hypertrophic zones.

Bone age

Bone age is used as clinical tool to assess the point at which a child has arrived in his or her skeletal development

- **X- rays of the foot and knee for neonates**
- **X- rays of the wrist and hand for older children**

(the x-ray is estimate by the methods of Greulish and Pyle, and Tanner and Whitehouse. Greulich and Pyle have definied stages of development of individuals bones in the hand and wrist and the median ages of their occurrence. Next they have selected representative x-rays by sex and age. Since there are always some individual bones that deviate from the median, each standard x-ray is accompanied by a table indicating the „age" of individual bones)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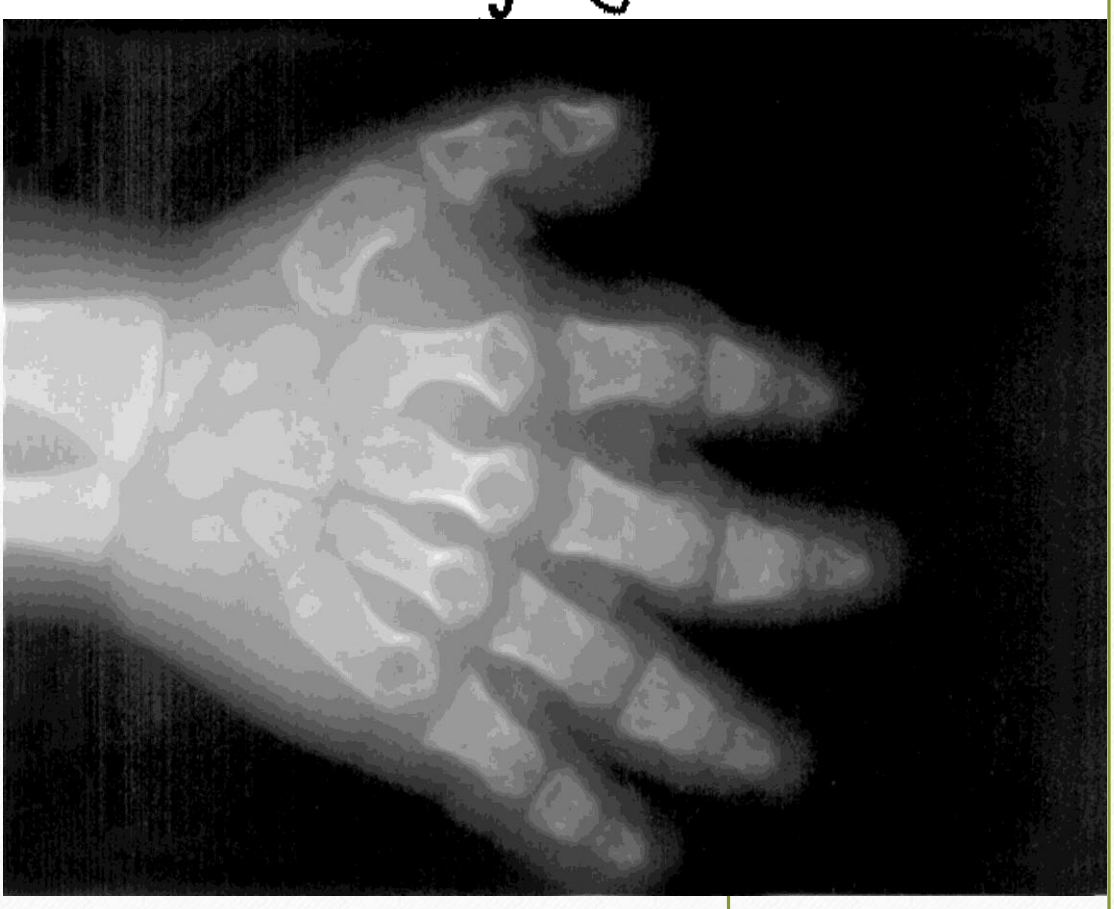


Height : 3'90"
3'30"

Causes of short stature according to the ESPE classification -1-

A Primary growth disorders

A1 Clinically defined syndromes

- Turner syndrome
- Cornelia de Lange syndrome
- DiDeorge syndrome (velocardiofacial syndrome)
- Down syndrome
- Noonan syndrome
- Prader-Willi-Labhart syndrome
- Von Recklinghausen's disease (neurofibromatosis type 1)
- Silver-Russell syndrome

Causes of short stature according to the ESPE classification -2-

A2 Small for gestational age with failure of catch-up growth

- IGF-I deficiency, IGF resistance
- Due to known cause, e.g. prenatal infections, drugs,
- smoking, alcohol
- Idiopathic

Causes of short stature according to the ESPE classification -3-

A3 Skeletal dysplasias

- Achondroplasia
- Hypochondroplasia
- Dyschondrosteosis (Leri-Weill and other defects in the
- SHOX gene)
- Osteogenesis imperfecta I–VI
- Mucopolysaccharidosis (type IH, IS, II–VII)
- Mucolipidosis (type II and III)

A4 Dysplasias with defective mineralization

Causes of short stature according to the ESPE classification -4-

B Secondary growth disorders

B1 Insufficient nutrient intake (malnutrition)

B2 Disorders in organ systems

- Cardiac disorders
- Pulmonary disorders, e.g. cystic fibrosis
- Liver disorders
- Intestinal disorders, e.g. Crohn's disease, malabsorption syndromes
- Short bowel syndrome
- Renal disorders, e.g. Fanconi syndrome, renal acidosis
- Chronic anemia

Causes of short stature according to the ESPE classification -5-

B3 Growth hormone deficiency (secondary IGF-I deficiency)

- Idiopathic
- Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4,GHRHR, GH)
- Associated with syndromes or cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
- Associated with prenatal infections, e.g. rubella
- Acquired (craniopharyngioma, other pituitary tumors, e.g. germinoma, hamartoma)
- Head trauma
- Central nervous system infections
- Granulomatous diseases, e.g. histiocytosis

Causes of short stature according to the ESPE classification -6-

B4 Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)

- Bioinactive growth hormone
- Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome, Laron syndrome)
- Abnormalities of GH signal transduction, e.g. STAT5B defect
- ALS (acid-labile subunit) deficiency
- IGF-I deficiency
- IGF resistance (IGF1R defects, postreceptor defects)

Causes of short stature according to the ESPE classification -7-

B5 Other endocrine disorders

- Cushing syndrome
- Hypothyroidism
- Leprechaunism
- Diabetes mellitus (poorly controlled)
- Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, congenital adrenal
- hyperplasia, exogenous estrogens or androgens

Causes of short stature according to the ESPE classification -8-

B6 Metabolic disorders

- Disorders of calcium and phosphorus metabolism
- Disorders of carbohydrate metabolism
- Disorders of lipid metabolism
- Disorders of protein metabolism

Causes of short stature according to the ESPE classification -9-

B7 Psychosocial

- Emotional deprivation
- Anorexia nervosa
- Depression

B8 Iatrogenic

- Systemic glucocorticoid therapy
- Local glucocorticoid therapy (inhalation, intestinal, other)
- Other medication
- Treatment of childhood malignancy, total body irradiation, chemotherapy, Other specified iatrogenic causes

Causes of short stature according to the ESPE classification -10-

C Idiopathic short stature

- *C1 Familial (idiopathic) short stature*
- *C2 Non-familial (idiopathic) short stature*

Dysmorphic features in short stature and associated syndrome

Dysmorphic feature	Associated syndrome
Short nose with anteverted nostrils	Smith-Lemli-Opitz
Continuous eyebrows	Cornelia de Lange
Absence of adipose tissue	Leprechaunism
Alopecia	Progeria
Ambiguous genitalia/ abnormal genitalia	Mixed gonadal dysgenesis/ 46,XY/45X chromosomal mosaicism/Smith-Lemli-Opitz/ Aarskog
Asymmetry of the face/ arms/legs	Russell-Silver
Bicuspid aortic valve	Turner
Bird-headed face	Seckel
Broad thumbs and toes	Rubinstein-Taybi

Semith-Lemli-Opitz

autosomal recessive caused by a deficiency of the enzyme 3 beta-hydroxysterol-delta 7-reductase (7-dehydrocholesterol-delta 7-reductase, the final enzyme in the sterol synthetic pathway that converts 7-dehydrocholesterol (7DHC) to cholesterol.

Cleft lip and/or palate	Growth hormone deficiency
Clinodactyly	Russell-Silver
Coarctatio aortae	Turner
Cryptorchism	Noonan, Prader-Willi, Rubinstein-Taybi
Cubiti valgi	Turner
Digital V missing/no nails	Coffin-Siris
Disproportion	Skeletal dysplasias
Elfin face	Williams
Epicanthus	Down
High arched palate	22q11 deletion syndrome, SHOX
Hirsutism	Coffin-Siris, Cornelia de Lange
Hypogonadism	Robinow, Smith-Lemli-Opitz
Hypoplastic nipples	Turner
Hypospadia	46,XY/45X chromosomal mosaicism
Inverted nipples	Turner
Lymphedema (congenital)	Turner
Madelung deformity	Leri-Weill, SHOX abnormalitie
Micropenis	Prader-Willi, growth hormone deficiency
Muscular hypotonia	Down, Prader-Willi

Nail convexity/dysplasia	Turner
Nevi (multiple)	Turner
Ptosis	Aarskog, Dubowitz, Noonan, Turner
Pulmonary valvular stenosis	Noonan
Shawl scrotum	Aarskog
Short 4th and 5th meta-carpals	Pseudohypoparathyroidism
Single central incisor	Growth hormone deficiency
Small hands/feet	Prader-Willi
Telangiectasia in face	Bloom
Triangular face	Russell-Silver
Webbed neck	Noonan, Turner

1. Silver Russell syndrome

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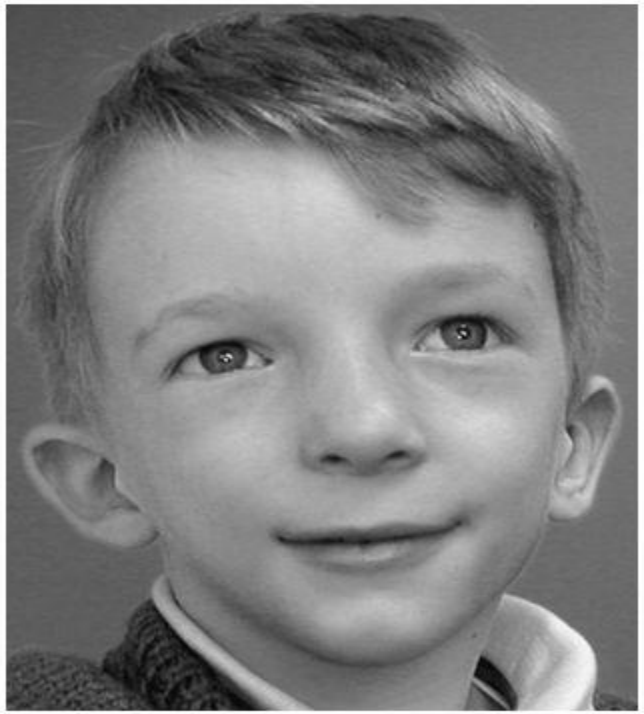


Chromosomes 7 and 11

- Growth retardation before and after birth
- Large head compared to rest of the body
- Prominent head, narrow chin
- 5th finger clinodactyly
- hemihypoplasia

Silver-Russell Syndrome

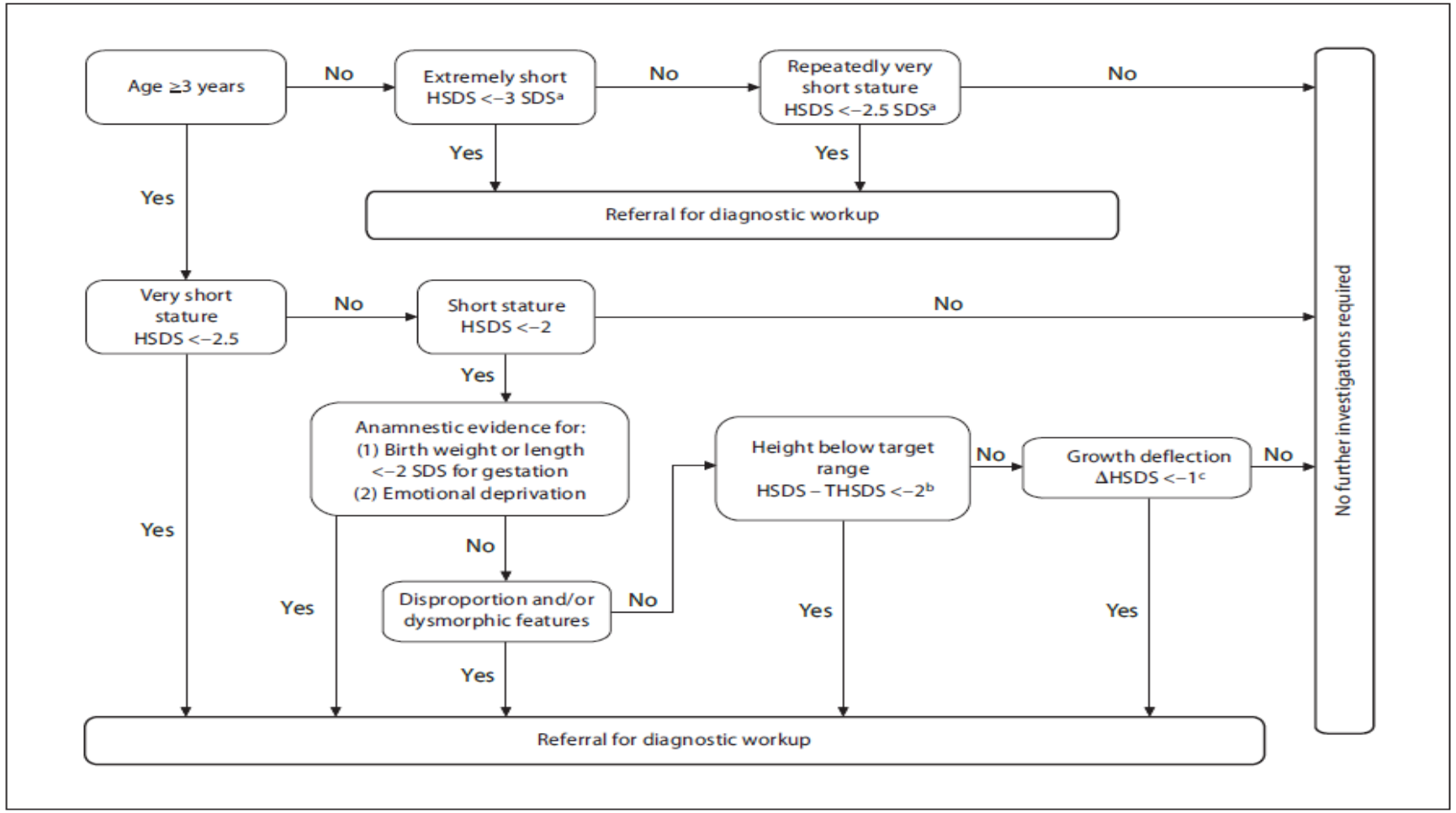
Silver-Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder, characterized by severe pre/postnatal growth retardation, characteristic facies, skeletal asymmetry, and other congenital anomalies. The incidence is estimated as 1:50,000–1:100,000 live births.

GENETIC/BASIC DEFECTS

1. Inheritance
   a. Sporadic occurrence in majority of cases
   b. 19% of cases with more than one affected individuals in the family, providing evidence for a genetic cause
   c. A genetically (and clinically) heterogeneous disorder
      i. Autosomal recessive (17.4%)
      ii. Autosomal dominant (8.7%)
      iii. X-linked dominant (74%)
2. Chromosomal basis
   a. Small number of cases with Silver-Russell syndrome reported in association with numerous chromosomal abnormalities
      i. R(15) and deletion of 15q
      ii. Diploid–triploid mixoploidy
      iii. 45,X/46,XY
      iv. XXY
      v. Trisomy 18 mosaicism
      vi. Del(8)(q11-q13)
      vii. Del(18p)
      viii. Dup(1)(q32.1-q42.1)
      ix. Dup(7p12.1-p13)
      x. Distal chromosome 17q
         a) Balanced translocation (17;20)(q25;q13) inherited from clinically normal father
         b) *De novo* translocation (1;17)(q31;q25) with breakpoint recently cloned and localized to 17q23.3-q24
         c) Heterozygous deletion of the chorionic somatomammotrophin hormone 1 (*CSH1*) gene located within the growth hormone and CSH gene cluster on 17q24.1. The deletion was inherited from the father who appeared clinically normal but had short stature
   b. Maternal uniparental disomy (UPD) for chromosome 7 (about 7–10% of cases)
      i. Inheritance of both chromosomes 7 from the mother
      ii. A possible novel imprinted region at 7p12-p14, 7q32, and 7q31-ter: UPD can disrupt the balance between imprinted genes and thereby lead to phenotypic manifestations
      iii. Strong evidence of disruption of imprinted gene expression rather than mutation of a recessive gene underlying the Silver-Russell phenotype in these cases
   c. The majority of the cases, however, have a normal karyotype

CLINICAL FEATURES

1. Diagnostic criteria: Presence of three major features plus one or more minor features is generally required for a positive diagnosis.
   a. Major criteria
      i. Low birth weight (intrauterine growth retardation)
      ii. Proportionate short stature (postnatal growth retardation): mature height about –3.6 standard deviation scores in both sexes
      iii. Small triangular face
      iv. Fifth finger clinodactyly
   b. Minor criteria
      i. Relative macrocephaly due to sparing of cranial growth
      ii. Ear anomalies
      iii. Skeletal asymmetry (face, limb, or body)
      iv. Brachydactyly of the fifth fingers
      v. Bilateral camptodactyly with terminal interphalangeal contractures
      vi. Syndactyly
      vii. Transverse palmar crease
      viii. Downward slanting corner of the mouth
      ix. Muscular hypotrophy/hypotonia
      x. Motor/neurological delay
      xi. Irregular spacing of the teeth
      xii. Café-au-lait spots
      xiii. Precocious puberty
      xiv. Squeaky voice
      xv. Genital abnormalities
      xvi. Speech delay
      xvii. Feeding difficulties
2. Other manifestations
   a. Significant cognitive impairment (50%)
   b. Gastrointestinal symptoms (77%)
      i. Gastroesophageal reflux disease (34%)
      ii. Esophagitis (25%)
      iii. Food aversion (32%)
      iv. Failure to thrive (63%)
   c. Skeletal anomalies
      i. Large anterior fontanelle (delayed closure)
      ii. Absence of asymmetry
      iii. Syndactyly of the toes
   d. Genitourinary anomalies
      i. Hypospadias
      ii. Posterior urethral valves



In chlidren < 3y.o.

Wilma Oostdijk, Floor K. Grote, Sabine M.P.F. de Muinck Keizer-Schrama , Jan M. Wit **Diagnostic Approach in Children withShort Stature.** Horm Res 2009;72:206–217

Growth hormone deficiency

- Congenital

Idiopatic GH deficiency, or with:

- other pituitary hormone deficiences

- with midline defects

- pituitary agenesis, hypoplasia, aplasia and stalk interruption, ectopic anterior pituitary

With gene deficiency GH, GHRH

Table 1 Human mutations causing abnormal hypothalamo–pituitary development and function.

Gene	Phenotype	Inheritance
Combined pituitary hormone deficiency (*CPHD*)		
POU1F1	GH, TSH, prolactin deficiencies; usually severe; small or normal AP	Recessive, dominant
PROP1	GH, TSH, LH, FSH, prolactin deficiencies; evolving ACTH deficiency; small, normal or enlarged AP	Recessive
Specific syndrome		
HESX1	IGHD, CPHD, septo-optic dysplasia; APH, EPP, absent infundibulum, ACC	Recessive, dominant
LHX3	CPHD (GH, TSH, LH, FSH, prolactin deficiencies), short neck, limited rotation; small, normal or enlarged AP, short cervical spine	Recessive
LHX4	CPHD (GH, TSH, ACTH deficiencies); small AP, EPP, cerebellar abnormalities	Dominant
SOX3	IGHD and mental retardation, panhypopituitarism; APH, infundibular hypoplasia, EPP	X Linked
SOX2	Hypogonadotrophic hypogonadism; APH, bilateral anophthalmia/microphthalmia, abnormal corpus callosum, learning difficulties, oesophageal atresia, sensorineural hearing loss	*De novo*
TBX19	Neonatal ACTH deficiency	Recessive

AP(H), anterior pituitary (hypoplasia); EPP, ectopic posterior pituitary; ACC, agenesis of corpus callosum.

Kelberman and Mehul Tulsidas Dattani . *Hypothalamic and pituitary development: novel insights into the aetiology.*
Daniel European Journal of Endocrinology (2007) 157 S3–S14

Septo-optic dysplasia /HESX1, SOX2 mutation/

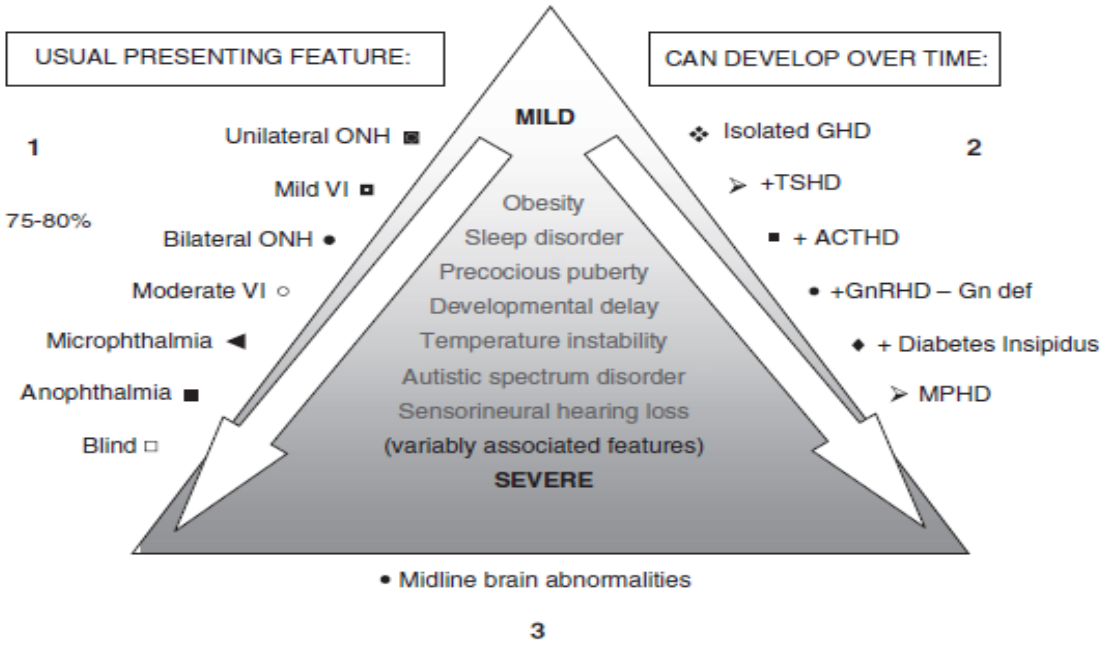


Figure 1 Spectrum of severity of the triad of abnormalities found in septo-optic dysplasia and the variably associated clinical features.

EA Webb and MT Dattani *Septo-optic dysplasia.* European Journal of Human Genetics (2010) 18, 393–397

European Journal of Human Genetics

Onset of pituitary insufficiency Clinical features 1

- **<u>GH deficiency</u>: in neonates hypoglycemia, children - short stature, in adults - decreased sence of well-being, lower health-related quality of life, decreased muscle mass, increased fat mass**
- **<u>TSH deficiency</u>: prolonged jaundice, cold intolerance, dry skin, mental dullnes, bradycardia, constipation, anemia (like in primary thyroid failure but clinical changes are less severe and goiter is absent)**

Onset of pituitary insufficiency Clinical features 2

- **ACTH deficiency: hypoglycemia, weakness, nausea, vomiting, anorexia, weight loss, fever, hypotension (like in primary adrenal failure)**
- **PRL deficiency- symptom of PRL deficiency is failure of postpartum lactation**
- **Gonadotropin deficiency: micropenis, hypogonadism, oligomenorrhea, amenorrhea in women in men eunochoid apperance**

GH deficiency

Key elements that may indicate GH deficiency are:

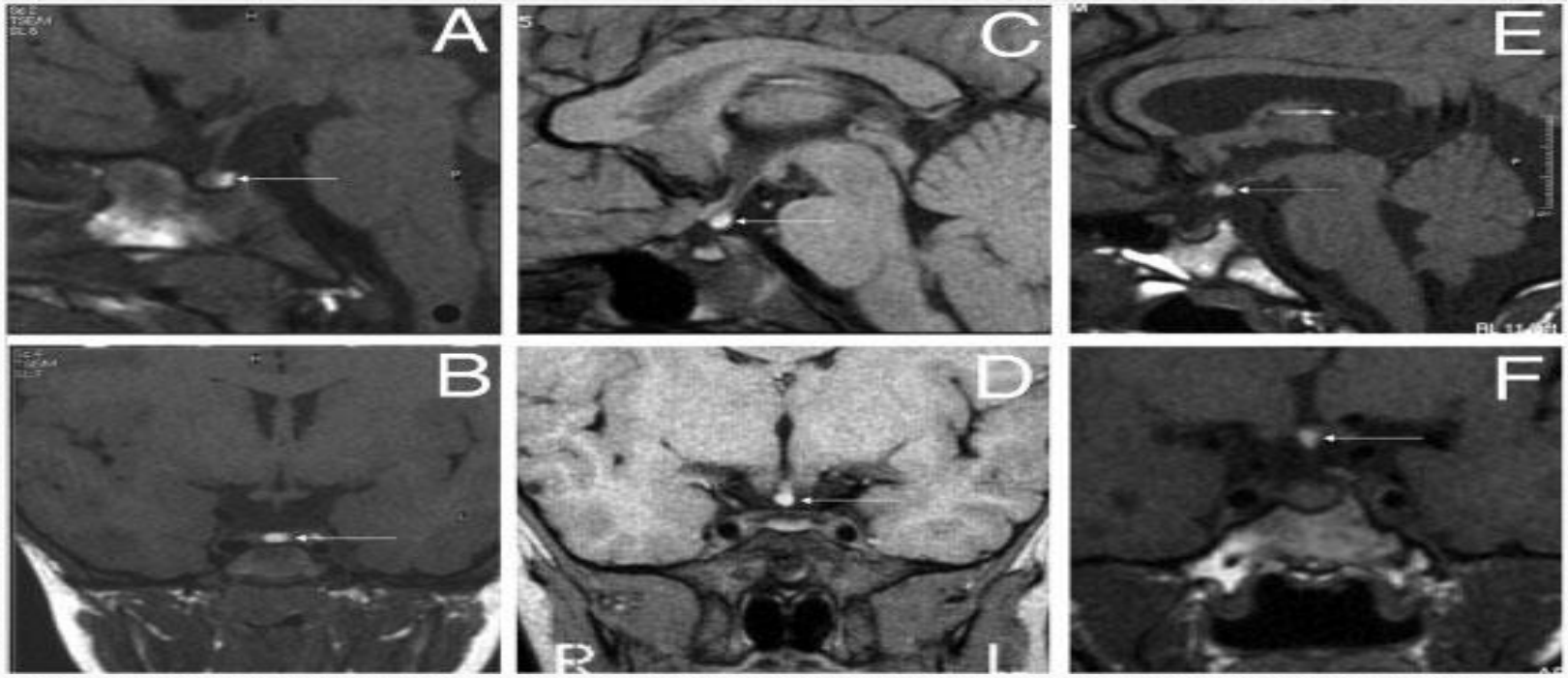
- Height more than 2 SD below the mean.
- Neonatal hypoglycemia, micropenis, prolonged jaundice, or traumatic delivery.
- A peak GH concentration after provocative GH testing is less than 10 ng/ml.
- Consanguinity and/or a family member with GH deficiency.
- Midline defects, pituitary hypo- or aplasia.
- Deficiency of other pituitary hormones: TSH, PRL, LH/FSH and/or ACTH deficiency.

GH deficiency

Biochemical evaluation of GH deficiency:

As growth hormone is secreted in a pulsatile manner, with little serum GH at any given time, three methods have been used to assess the adequacy of GH secretion:

1. Stimulation testing: GH provocation utilizing arginine, clonidine, glucagon, L-Dopa, insulin, etc. This practice generally measures pituitary reserve-or GH secretory ability-rather than endogenous secretory status.
2. GH-dependent biochemical markers: IGF1 and IGFBP3: Values below a cut-off less than -2 SD for IGF1 and/or IGFBP3 strongly suggest an abnormality in the GH axis if other causes of low IGF have been excluded. Age and gender appropriate reference ranges for IGF1 and IGFBP3 are mandatory.
3. Blood sampling at frequent intervals designed to quantify physiologic bursts of GH secretion (e.g. 24-hour or overnight GH sampling)



Cerebral MRI (T1-weighted images).
A, Sagittal slice; B, coronal slice; normal morphology of anterior pituitary and pituitary stalk is seen. The hyperintense signal of the posterior pituitary is in the normal location.
C, Sagittal slice; D, Coronal slice; a normal anterior pituitary with a thin pituitary stalk is seen. The ectopic posterior pituitary hyperintense signal is located along the stalk (at a proximal level of the pituitary stalk; *arrow*).
E, Sagittal slice; F, coronal slice; hypoplastic anterior pituitary with no visible pituitary stalk after gadolinium injection. The ectopic pituitary hyperintense signal is at the median eminence (*arrow*).

Treatment

- GH deficiency is treated with biosyntetic recombinant DNA-derived GH.

Hyposomatotropism hypersomatotropic

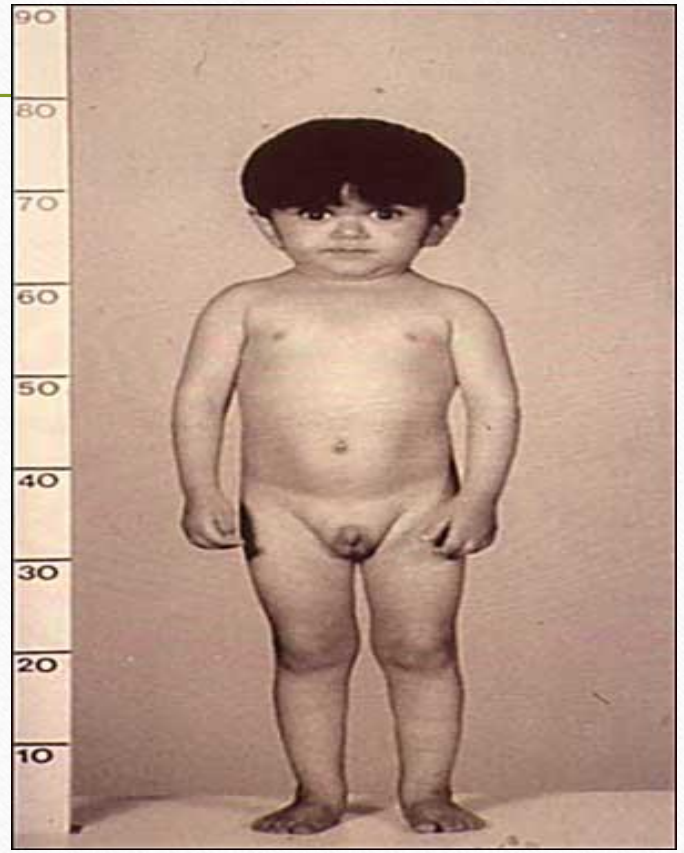
Increased GH and decreased IGF-1

GH insensitivity can be caused by genetic defects in GHR, Stat5B, IGF1 (regulatory gen IGF1, IGF1 receptor, post-translational pathway), deficient of IGFBP3/IGFALS complex

Laron dwarfism

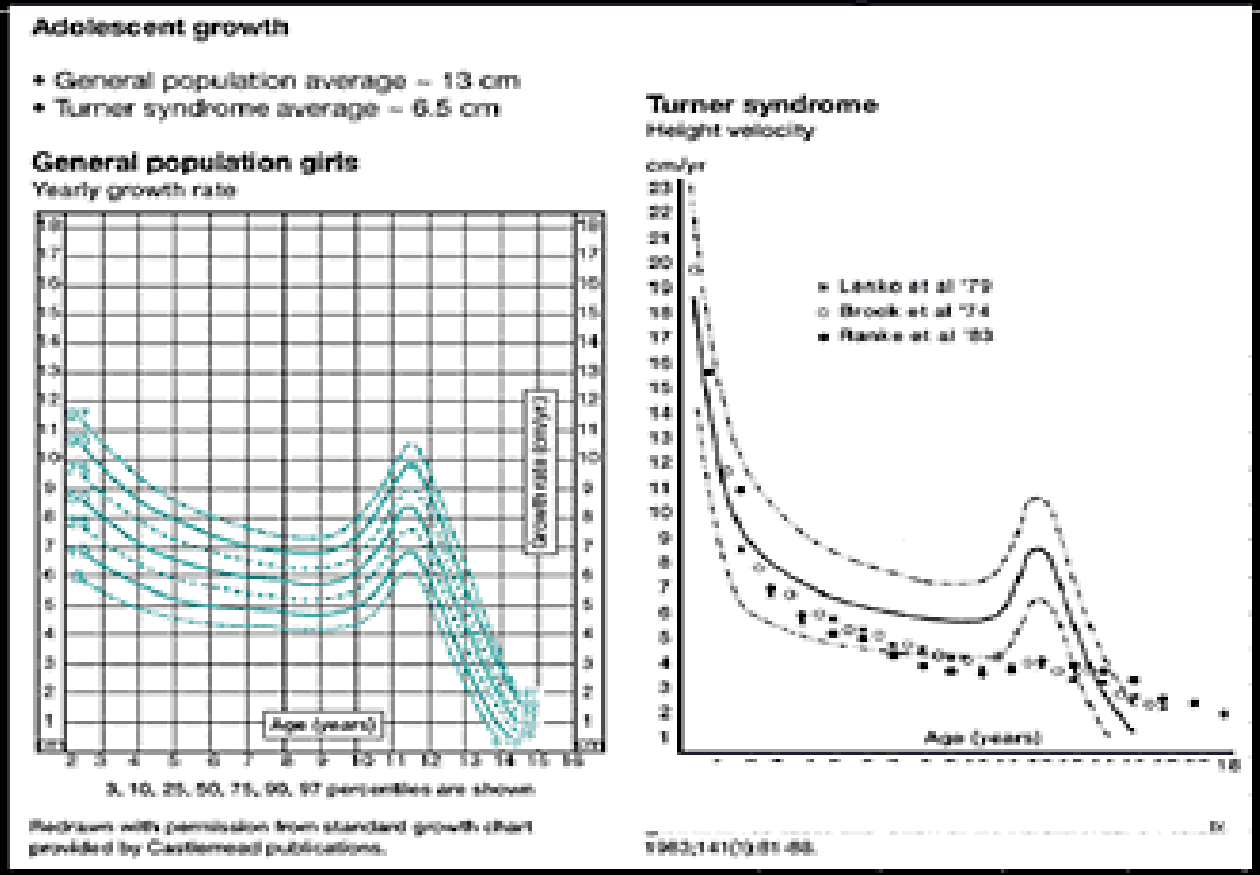
Clinical features:

Acromicria
Obesity
High-pitched voice
Blue sclerae
Discolored crowded teeth
Hypoglycemia
Sexual maturation
Final heights of adults range from 108-136 cm
Treatment:- administration of recombinant IGF-1



Turner syndrome

Height Velocity: Normal vs Turner Syndrome



Ranke MB, et al. *Eur J Pediatr*. 1983;141(2):81-88.

Turner syndrome

- **Sex:** Turner syndrome only occurs in females.
- Noonan syndrome, sometimes inappropriately called male Turner syndrome, can occur in males or females. It is an autosomal dominant disorder and is unrelated.
- **Age:** As a chromosomal disorder, Turner syndrome is present at conception or following the first cell division, and it remains throughout life.
- Gonadotropins, particularly follicle-stimulating hormone (FSH), may be elevated at birth, although not reliably enough for use in excluding the diagnosis. They are gradually suppressed by about 4 years of age, only to rise to menopausal levels after age 10 years.

Turner syndrome

Approximately 95% of individuals with Turner syndrome have both short stature and signs of ovarian failure on physical examination.

- **Short stature.** Before age 11 years, some girls have height and growth rates that are well within the normal range, but heights are below the 50th percentile.
- **Ovarian failure:** Suspect ovarian failure in girls who have no breast development by age 12 years or who have not started menses by age 14 years. Elevated levels of luteinizing hormone (LH) and FSH confirm ovarian failure.

Turner syndrome

- **Pubic hair:** Pubic hair development is normal.
- **Nevi:** Excessive numbers of nevi- increased risk of keloid formation.
- **Webbed neck:** Lymphedema in utero can cause a broad neck and a low or indistinct hairline.
- **Cubitus valgus** (increased carrying angle): This is a common skeletal anomaly in girls due to abnormal development of the trochlear head. Other anomalies include Madelung deformities and short fourth and fifth metacarpals or metatarsal.

Turner syndrome

- **Shield chest:** The chest appears to be broad with widely spaced nipples. This may be caused in part by a short sternum.
- **Lymphedema:** It may be present at any age and is one finding that can suggest Turner syndrome. Lymphedema is the cause of other anomalies, such as the webbed neck and low posterior hairline.
- **Eye:** Ptosis, strabismus, amblyopia, and cataracts are more common in girls with Turner syndrome. Epicanthal folds can be present. Red-green color blindness is an X-linked condition and would be expected to occur in girls with Turner syndrome as commonly as it does in males.
- **Ears:** otitis media is more common

Turner syndrome

- Gastrointestinal bleeding
- Hip dislocation: Infants have a higher incidence of congenital hip dislocation.
- Scoliosis: This occurs in 10% of adolescent girls with Turner syndrome and may contribute to short stature. Scoliosis screening is essential.
- Hypertension: Blood pressure elevations may be caused by coarctation of the aorta or renal anomalies but often occur even in the absence of such findings.

Turner syndrome

- Thyroid: As many as half of patients have positive antithyroid antibodies, and 10-30% develop hypothyroidism. This is often associated with thyroid enlargement.
- Cutis laxa
- Prenatal signs: Most concepti with a 45 X karyotype spontaneously abort. Most, if not all, of those who survive to birth are suspected to have mosaicism for a normal cell line. Turner syndrome may be diagnosed prenatally by amniocentesis or chorionic villous sampling.

Turner syndrome

- Diagnosis
  - A karyotype is required for diagnosis. Diagnosis is confirmed by the presence of a 45 X cell line or a cell line with deletion of the short arm of the X chromosome (Xp deletion).
  - The buccal smear for Barr bodies is obsolete.
- Y chromosome
  - Patients with 45, X/46, XY mosaicism may have mixed gonadal dysgenesis and are at a high risk for gonadoblastoma. These patients may require a prophylactic gonadectomy to prevent death from malignancy.
  - Patients with ring chromosomes or fragments of chromosomes should be examined for Y chromosomal material for the same reason.

Turner syndrome

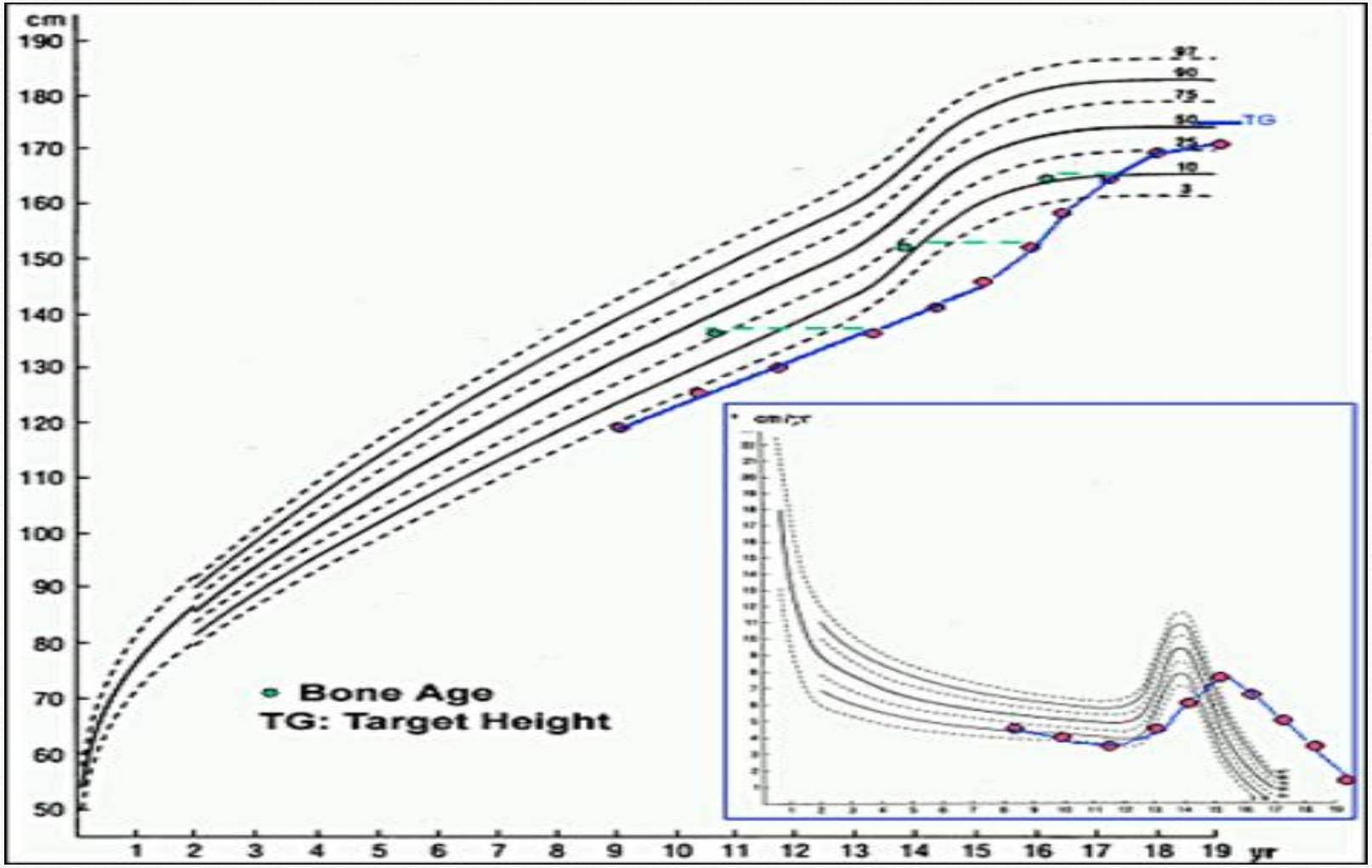
- Gonadotropins
  - Both LH and FSH may be elevated in untreated patients younger than 4 years. Gonadotropins are later suppressed to normal or near-normal levels, only to rise to menopausal levels after 10 years of age.
  - Obtain both LH and FSH levels prior to initiating estrogen replacement therapy.
- Thyroid function tests
  - Because of the high prevalence of hypothyroidism in Turner syndrome, obtain thyroid function tests at diagnosis.
  - Thyroid-stimulating hormone (TSH) measurements should be repeated every 1-2 years or if symptomatic because patients may develop hypothyroidism at a later age.
- Glucose metabolism

Growth disorders
growth retardation *classification 5*

- Familial short stature - this is not disorder. The children have normal growth velocities, and their height curve parallels the third percentile (parents with short stature)

Constitutional slow growth- normal growth velocities. GH secretions are in normal range.

Constitutional slow growth and development



Excessive growth

- Familial tall stature
- Metabolic
  - homocystinuria
- Syndromes
  - Cerebral gigantism
  - Beckwith-Wiedeman syndrome
  - Marfan syndrome
  - Klinefelter syndrome
  - XYY syndrome

Excessive growth

Marfan syndrome

- **Causes**

Marfan Syndrome is caused by a defect in the gene that determines the structure of fibrillin, a protein that is an important part of connective tissue. The defective gene can be inherited.

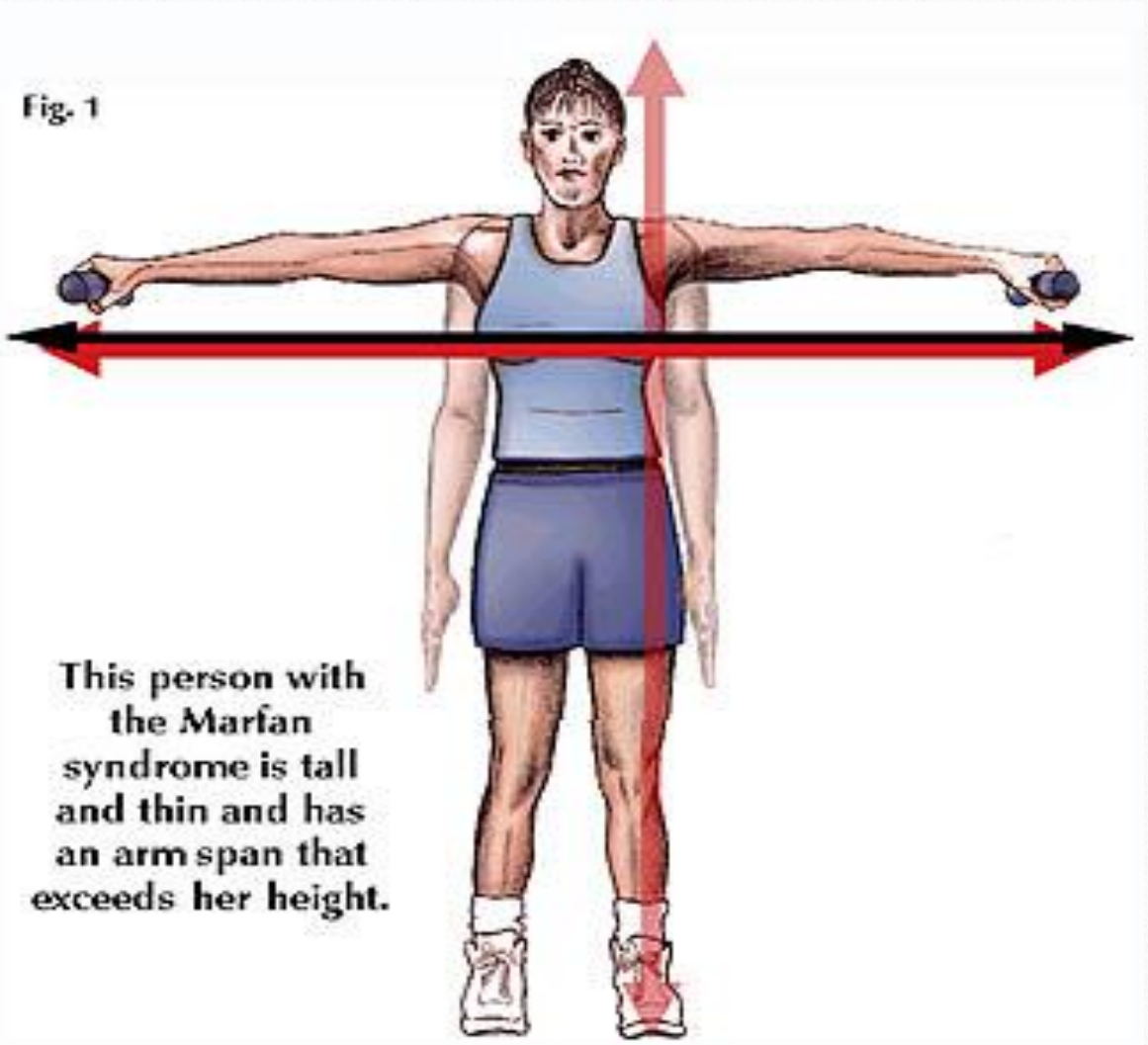
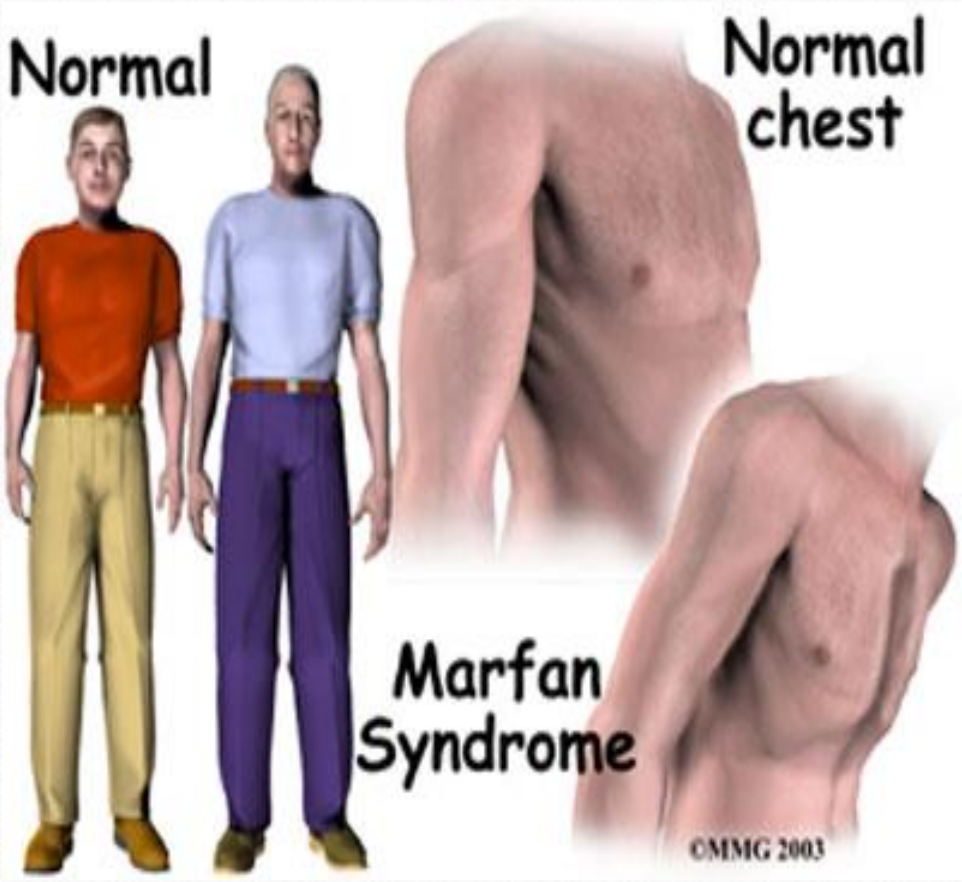


Fig. 1
This person with the Marfan syndrome is tall and thin and has an arm span that exceeds her height.


Normal hands
Marfan Syndrome
Elongated finger and arm bones


Normal
Normal chest
Marfan Syndrome
©MMG 2003

Excessive growth

Sotos syndrome

- Sotos syndrome was first described by Sotos et al. (1964) in five children with overgrowth, acromegalic features, nonprogressive cerebral disorder with mental retardation and characteristic physiognomy.

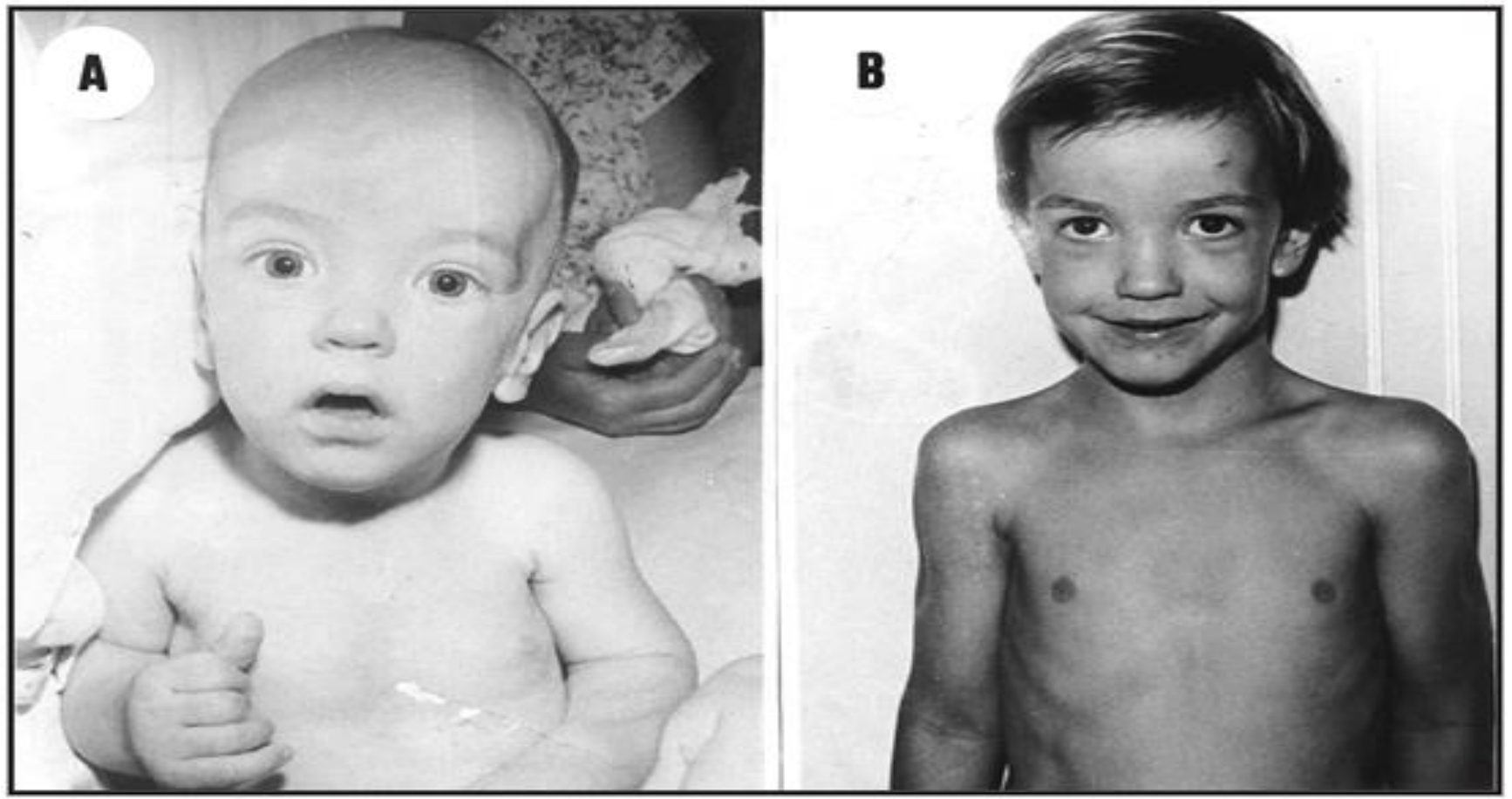
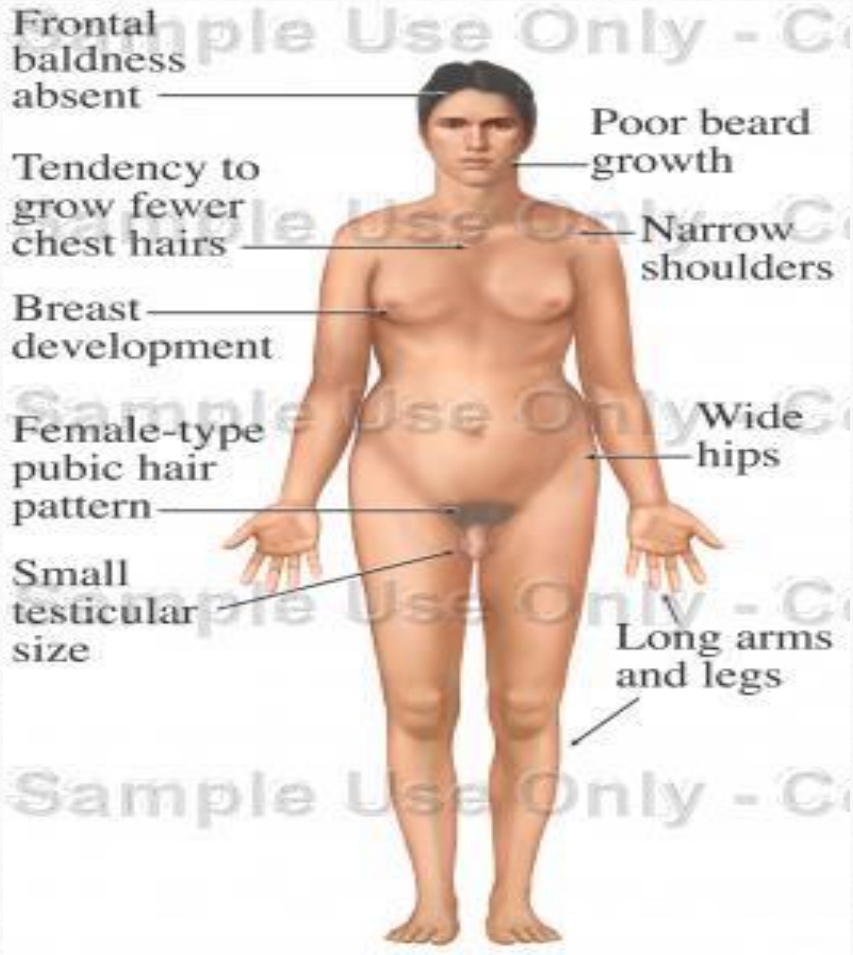


Fig 1. A) Patient 7 at age 6 months with appearance considered typical of Sotos syndrome. Note the prominent fore-head, telecanthus, epicanthic folds, flat nasal bridge, downslanting palpebral fissures and pointed chin. B) Same patient at age 4 years and 6 months. Photos published with written authorization given by the patient´s parents.

Klinefelter Syndrome 47XXY



- Klinefelter Syndrome occurs in 1 in 500 to 1 in 1000 live births. People with this disorder develop as males with subtle characteristics that become apparent during puberty. They are often tall and usually do not develop secondary sex characteristics such as facial hair, or underarm and pubic hair.
- Men and boys with Klinefelter Syndrome have a Y chromosome and 2 X chromosomes. This is an example of trisomy.

Excessive growth

Hormonal

- Excess growth hormone /GH- producting tumor/
- Precocious puberty
- CAH – congenital adrenal hyperplasia
- Gonadal tumor
- McCune-Albright syndrome
- Hypertyroidism
- Hyperinsulinemia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