Syndromic Short Stature

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INTRODUCTION

Syndrome: a group of specific unrelated features, develop together

Characteristics:

- **Chromosal abnormality**
- **Low birth**
- **Mental retardation**
- **Short stature**
- **Proportionate or disproportionate**

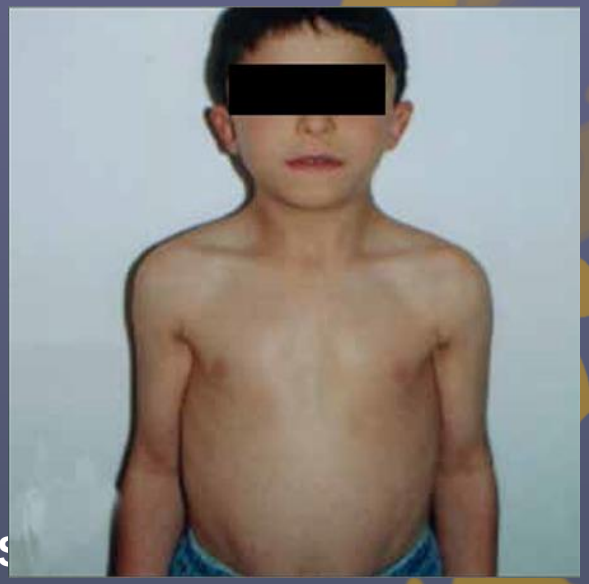
The most prevalent Syndromic SS:

- **Noonan syndrome (NS)**
- **Prader-Willi syndrome (PWS)**
- **Silver-Russell syndrome (SRS)**
- **Aarskog-Scott syndrome (ASS**

Usually, there is no growth hormone (GH) GH deficiency (GHD), but in some patients, a pathology in the GH/IGF-I axis can be detected

Syndromes with very short stature (and no skeletal dysplasia)	Syndromes with moderate short stature
Brachmann-de Lange syndrome	Smith-Lemli-Opitz syndrome
Rubinstein-Taybi syndrome	Kabuki syndrome
Silver-Russell syndrome	Williams syndrome
Mulibrey (Perheentupa) syndrome	Noonan syndrome
Dubowitz syndrome	Costello syndrome
Bloom syndrome	Cardio-facio-cutaneous syndrome
Johannson-Blizzard syndrome	Aarskog syndrome
Seckel syndrome	Robinow syndrome
Hallermann-Streiff syndrome	Opitz syndrome
Prader-Willi syndrome	Floating-Harbor syndrome

NOONAN SYNDROME1



Incidence :1/1000 to 1/2500 live births

Signs & symptomes:

1-Specific facial features :

- **Hypertelorism**
- **Ptosis**
- **Down-slanting palpebral fissures**
- **Low-set posteriorly rotated ears**
- **Short stature**

2-Cong. heart defects(PS, hypertrophic cardiomyopathy, AS
3-Chest and spinal deformities
4-Mild MR
5-Learning disabilities
6-Feeding difficulties in infancy
7-Cerebrovascular abnormalities
8-Abnormal pigmentation
9-Cryptorchidism(primary sertoli cell dysfunc. in male, so low fertility)
10-Lymphedema
11-Coagulation defects
12-Hearing defects
13-In newborn infants: generalized edema, webbed neck, CHD

NOONAN SYNDROME 2

Male/ famale :1

Inheritance:

- Sporadic 80%
- AD: 20%

Diagnosis :

1-typical face dysmorphology + 1 major sign or 2 minor signs
2-suggestive face dysmorphology + 2 major or 3 minor signs

Clinical characteristics	Major	Minor
Facial	Typical face	Suggestive face
Cardiac	Pulmonary valve stenosis and/or typical electrocardiography	Other defects
Height	<3rd centile	<10th centile
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First-degree relative with definitive diagnosis	First-degree relative with suggestive diagnosis
Other (mental retardation, cryptorchidism, lymphatic dysplasia)	All 3	Any of the 3

* Definite NS: typical face + one major or two minor clinical characteristics or suggestive face + two major or three minor clinical characteristics

The diagnostic criteria for NS (Van der Burght ; 1994)

NOONAN SYNDROME 3

Genetics

RAS/RAF- mitogen activated protein-kinase (MAPK) signaling pathway, implicated in growth factor-mediated cell prolif., different. & apoptosis

Differential diagnosis:

1. Cardio-facio-cutaneous (CFC) syndrome (OMIM115150)
2. Costello syndrome (OMIM218040)
3. Neurofibromatosis type 1 (OMIM162200)
4. Leopard syndrome (OMIM151100)
5. TS in girls

Average adult height:

- Females: 152 cm
- men:162 cm

NOONAN SYNDROME 4

Growth

1. Birth: weight and height are within normal limits
2. First year of life: rapid decline in ht SDS
3. After 2-4 y/o: mean ht; 3rd percentile until about 12 y/o in males and 10 y/o in females
4. Puberty: delayed by about 2 years with a low peak ht velocity

GH stimulation tests:

Nl responses but low IGF-1 and impaired spontaneous GH secr.

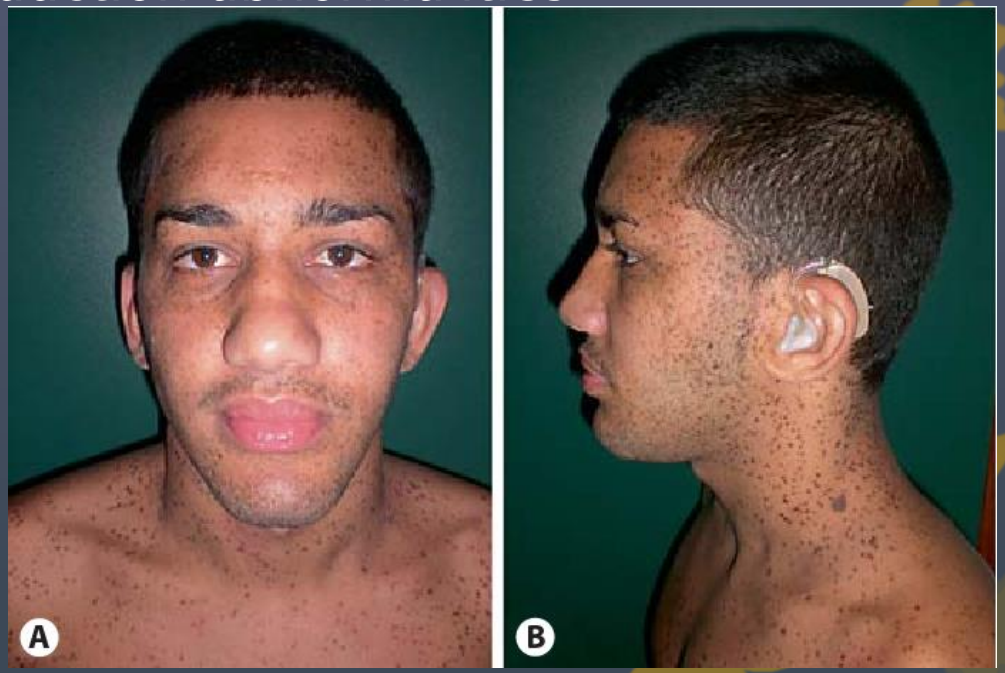
improved growth velocity with **rhGH** Tx

Final height :0.6 to 2.0 SDS over the controls

The benefit of **GH** Tx seems to be less marked in Pt with PTPN11 mut., suggesting a mode of GH insensitivity

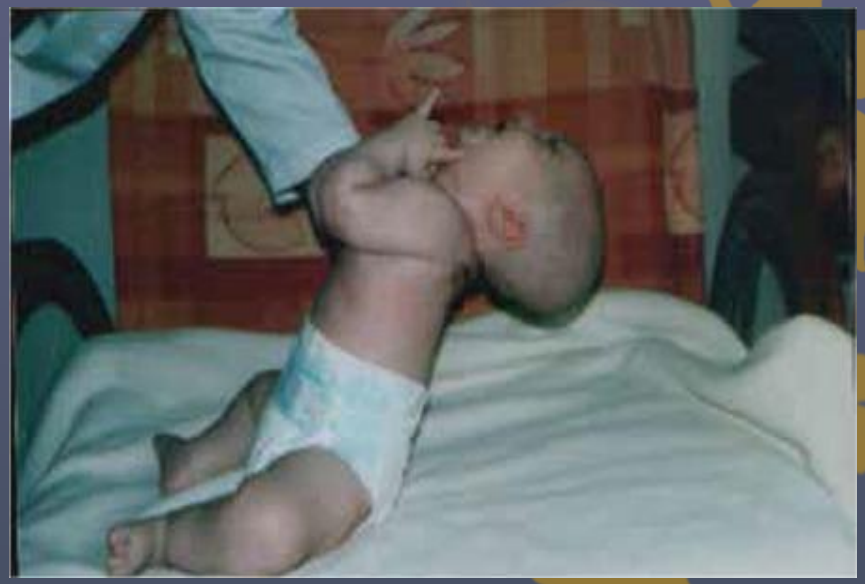
Leopard syndrome (multiple Lentigenes):

- Café-au-lait spots(early infancy & generalized multiple lentigines>5-6 y/o)
- AD
- Electrocardiographic conduction abnormalities
- Ocular hypertelorism
- Pulmonary stenosis
- Abnormal genitalia
- Growth Retardation
- Sensorineural Deafness



PRADER-WILLI SYNDROME 1

Prevalence : 1/10 000 - 1/30 000 live births



- Short stature
- Muscular hypotonia
- Abnormal body composition
- Progressive obesity
- Hypogonadism
- Mental retardation
- Behavioral abnormalities
- Respiratory and sleep disturbances
- Dysmorphic features
- Birth Wt & Lt : 15-20% smaller than their unaffected siblings
- Decreased fetal movement or delivery difficulties

PRADER-WILLI SYNDROME 2

1. Hypotonia : universal finding and improves over time
2. Delayed motor development and language milestones
3. Intellectual and/or learning disabilities as the child grows older
4. Obesity
5. Excessive weight gain
6. Hyperphagia and decreasing of satiety begin in early childhood
7. Characteristic facial features:
8. Strabismus
9. Small hands and feet
10. Scoliosis

Suggested clinical criteria to prompt DNA testing for PWS([ref:13]13[/ref])

Age of assessment	Features
Birth to 2 years	Hypotonia with poor suck
2-6 years	Hypotonia with a history of poor suck Global developmental delay
6-12 years	History of hypotonia with poor suck (hypotonia often persists) Global developmental delay Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
13 years to adulthood	Cognitive impairment, mental retardation (usually mild) Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled Hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features)

PRADER-WILLI SYNDROME 3

Genetics

- DNA testing:

1. Absence of one of the paternal gene in chro.15q11-q13 (70%)
2. Maternal uniparental disomy (UPD) of chromosome 15 (20-25%)
3. Microdeletions or epimutations in the 15q11-q13 region (2-5%)

Growth

- Short stature
- Hypogonadism
- GHD(80%) & absence of a pubertal growth spurt
- Hypothalamic dysfunction
- 1-2 y/o: ht decrease to <3rd centile
- 3-12 y/o: mild improvement (10th centile)
- After 12-14 y/o : ht & growth rate<5th centile
- Mean final height :

  Men: 155 cm

  Women: 148 cm

Tx

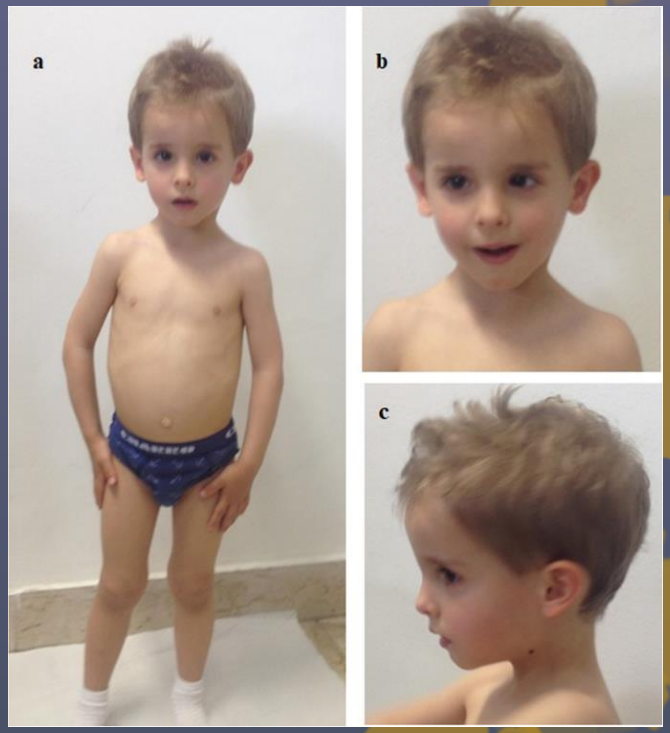
GH therapy

PRADER-WILLI SYNDROME 4

Other Specific Problems

- Increased body fat mass and decreased lean mass
- Decreased energy expenditure and resting metabolic rate
- Type 2 diabetes(mean age of 20 years)
- Hypertension
- Dyslipidemia
- Cardiopulmonary failure
- Sleeping disturbances
- Respiratory problems
- Hypotonia may lead to scoliosis
- Obstructive sleep apnea
- Insulin insensitivity & metabolic syndrome depending upon degree of obesity, body fat distribution, genetic background and medication central hypothyroidism : 25% (mean age of dx 2 y/o)

SILVER-RUSSELL SYNDROME 1



Incidence :

1 / 3000 - 1 / 100 000 live births

Major features :

1. Birth weight below or equal to -2 SD
2. Poor postnatal growth≤-2 SD
3. preservation of occipitofrontal circumference
4. Characteristic facial phenotype
5. Asymmetry(trunk, face, or limbs)

SILVER-RUSSELL SYNDROME 2

- Feeding difficulties in early childhood
- Excessive sweating in infancy
- Cleft palate
- Congenital heart disease
- Genital anomalies
- Limb defects
- Myoclonus-dystonia
- Short stature
- Delayed bone age
- Severe IUGR
- ↓ postnatal growth rate
- High forehead
- Preserved head circumference
- Small jaw
- Triangular face
- Clinodactyly/ Camptodactyly
- 5th middle or distal phalangeal hypolasia
- Hypospadias
- Skeletal asymmetry
- Lean body habitus
- Developmental delay
- Ivory epiphyses and second metacarpal pseudoepiphysis

SILVER-RUSSELL SYNDROME 3

Genetics

HETEROGENEOUS :

AD
AR
X-linked

1- IGF-2/H19 Hypomethylation (chr.11p15): Up to **50%**
2-Maternal UPD for chr.7: **10%**
3-Unknown genetic etiology: **40%**

Growth

- SGA
- Low birth weight (below -2 SDS) : 1900-2000 g
- Decreased postnatal height : Ht SDS-3.5 _ -4 by 4 y/o
- No postnatal catch-up growth
- Impaired Spontaneous GH secretion
- Delayed Bone age
- Mean adult height : males :151.2 cm
  females 139.9 cm

Tx: GH

AARSKOG-SCOTT SYNDROME (FACIOGENITAL SYND)1

Genetic: heterogeneous disorder

- X-linked
- AD
- AR

Clinical findings:

- Short stature (mild to moderate, disproportionate with acromelia)
- Facial, limb and genital anomalies
- Hypertelorism
- Umbilical hernia
- Shawl scrotum
- Hypospadias
- Undescended testes
- Skeletal dysplasia
- Mental retardation (mild or moderate): 30%
- Hyperactivity and attention deficit

AARSKOG-SCOTT SYNDROME (FACIOGENITAL SYND) 2

Dx:

- ✓ Round face
- ✓ Facial edema in children < 4 y/o
- ✓ Downward slanting palpebral fissures
- ✓ Short nose with anteverted nares
- ✓ Long filtrum
- ✓ Ocular hypertelorism with ptosis
- ✓ Maxillary hypoplasia
- ✓ Broad upper lip
- ✓ Widow's peak
- ✓ Mild pectus excavatum
- ✓ Cardiac defects
- ✓ Orthodontic problems
- ✓ Abnormal auricules
- ✓ Brachydactyly
- ✓ Clinodactily of the fifth finger
- ✓ Joint laxity
- ✓ Mild interdigital webbing
- ✓ Short broad hands and feet
- ✓ Bulbous toes
- ✓ Simian line
- ✓ Crease below the lower lip
- ✓ Myopathy

AARSKOG-SCOTT SYNDROME (FACIOGENITAL SYND) 3

Diff dx

- NS
- Pseudohypoparathyroidism
- Robinow's syndrome

Final height: <3rd centile(-2 _ -3SD)

GH stimulation test : normal

Tx: rhGH

.

Clinical features in Aarskog syndrome

Craniofacial	- Round face
	- Maxillary hypoplasia
	- Hypertelorism
	- Ptosis
	- Downward slanting palpebral fissures
	- Wide philtrum
	- Broad nasal bridge
	- Small nose with anteverted nares
	- Slight crease below the lower lip
	- Widow's peak
	- Ear helices abnormality
Hands and feet	- Syndactyly
	- Brachydactyly
	- Short/broad hands
	- Simian crease
	- Clinodactyly of 5th finger
	- Joint laxity
	- Broad, short, bulbous toes
	- Camptodactyly
	- Lymphedema
Genitalia	- Shawl scrotum
	- Macroorchidism
	- Hypospadias
	- Inguinal hernia
	- Prominent umbilicus
	- Cryptorchidism
Skeletal	- Short stature
	- Cervical vertebrae anomalies
	- Spina bifida occulta
	- Scoliosis
	- Pectus excavatum
Other	- Otism
	- Mild developmental delay

Conclusion

- **Syndromic disorders** with **short stature** are associated with a number of endocrinopathies as well as with developmental, systemic and behavioral problems
- **Growth failure** may be associated with aberrations in the **GH/IGF-1** axis or may be related to other specific problems
- A **Multidisciplinary Team Approach** is required for evaluation and treatment of these patients
- In most of **syndromic disorders**, **GH therapy** is widely accepted by clinicians, but some controversies exist with regard to GH dose, optimal age to begin GH therapy and possible adverse effects
- Before starting GH treatment, patients should be evaluated extensively with regard to **respiratory disturbances**, **glucose metabolism**, **malignancy risk** and other **undesirable effects** of this treatment


Thank you for
your attention