SMALL, SMALLER, SMALLEST—SILVER—RUSSELL TO PRIMORDIAL DWARFISM

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CAUSES OF GROWTH RESTRICTION

- **Bone disorders** - chondrodysplasias, rickets
- **Nutritional** - chronic infection, Celiac disease, Crohn’s disease, malabsorption
- **Congenital anomalies** - cardiac, renal, CNS
- **Metabolic** - renal acidosis, glycogen storage disease, etc.
- **Emotional** - psychosocial dwarfism
- **Endocrine** - hypothyroidism, hypopituitarism, Cushing’s disease
- **Intrauterine growth retardation** - Turner syndrome, small for dates, many syndromes, infection, chromosomal anomalies
- **Normal variation** - familial short stature, constitutional delay
HOW TO APPROACH SHORT STATURE?

1. Present at birth vs. later onset (i.e., IUGR, SGA, primordial)
2. Proportionate vs. non-proportionate – relative to what?
3. How short is short?
4. When falls off centiles *in utero*
5. Growth pattern after birth
IUGR – Intrauterine Growth Retardation
SGA – Small for Gestational Age
PRIMORDIAL – Prior to Birth

- IUGR = SGA = PRIMORDIAL
- Below the 3rd centile for gestational age
- How far below?
- Relative centiles of OFC, length, and weight
NATURE’S RULE OF THUMB

OFC > LENGTH > WEIGHT

i.e., Preserve the brain if you can
RELATIVE TO WHAT AT WHAT AGE?

- OFC, length/height, weight
  FOR AGE (and to each other)

- OFC, length/height, weight
  FOR HEIGHT AGE

- OFC, length/height, weight
  FOR BONE AGE
<table>
<thead>
<tr>
<th>Percentile</th>
<th>Other anomalies</th>
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<tbody>
<tr>
<td><strong>Body</strong></td>
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<td>Height</td>
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<td>Lower segment</td>
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<td>Upper segment</td>
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<td>L/L segment ratio</td>
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<td>Chest circumference</td>
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<td>Intertrochanteric distance</td>
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<td>Sternal length</td>
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<td><strong>Craniofacies</strong></td>
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<td>Head circumference (DFC)</td>
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<td>Anterior fontanelle</td>
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<td>Facial width</td>
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<td>Facial height</td>
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<td>Outer canthus distance</td>
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<td>Interpupillary distance</td>
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<td>Palpebral fissure length</td>
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<td>Nasal length</td>
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<td>Nasal protrusion</td>
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<td>Nasal width</td>
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<td>Ear length</td>
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<td>Ear width</td>
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<td>Ear position</td>
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<td>Ear rotation</td>
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<td>Planocone length</td>
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<td>Mouth width</td>
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<td><strong>Limbs</strong></td>
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<td>Hand length</td>
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<td>Palm length</td>
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<td>Palm width</td>
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<td>Finger length</td>
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<td>Elbow angle</td>
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<td>Foot length</td>
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<td>Foot width</td>
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<td><strong>Genitalia</strong></td>
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<td>Labial site</td>
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<td>Testicle size</td>
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<td>Penis length</td>
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<td>Development assessment</td>
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Summary of unusual/abnormal measurements

Any special techniques or instruments for measuring

Dermatoglyphics done: Yes/No  Photographs done: Yes/No  X-ray: Yes/No  Bone age done: Yes/No
PROPORTIONAL VS. NON-PROPORTIONATE
(MIDGET) (DWARF)

- Length/height compared to span
- Upper/lower segment
- Proximal, middle, distal
HERE WE ARE TALKING ABOUT:

- IUGR/SGA (prenatal)
- Relatively proportionate short stature postnatally
- Very, very small types of syndromes

Centiles have little meaning way, way, below 3^{rd} centile!

>>>3^{rd} centile
Significant IUGR
Relatively PROPORTIONATE/POST NATAL SHORT STATURE DISORDERS

1. Bloom*
2. Dubowitz
3. Floating Harbor
4. MOPD II*
5. Mulibrey*
6. Silver-Russell/Russell-Silver***
7. SHORT
8. 3-M*

Also: Chromosomal, CPM, and teratogens
<table>
<thead>
<tr>
<th>Layer</th>
<th>Term Delivery</th>
<th>Adult Height</th>
<th>Ofc</th>
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<tbody>
<tr>
<td>A</td>
<td>FLOATING HARBOR</td>
<td>2460 gm 46.8 cm</td>
<td>130 cm-140 cm Slow growth</td>
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<tr>
<td></td>
<td>MULIBREY</td>
<td>2400 gm 45 cm</td>
<td>2nd best 150 cm</td>
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<td></td>
<td>DUBOWITZ</td>
<td>2300 gm 45 cm</td>
<td>4th best 146 cm</td>
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<tr>
<td></td>
<td>SHORT</td>
<td>2200 gm 45 cm</td>
<td>154 cm Best growth</td>
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<tr>
<td></td>
<td>3-M</td>
<td>2100 gm 40 cm</td>
<td>120 cm-136 cm</td>
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<td></td>
<td>BLOOM</td>
<td>1850 gm 44 cm</td>
<td>3rd best 148 cm</td>
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<td>R-S heterogenous</td>
<td>1200 gm – 2500 gm 35 cm – 50 cm</td>
<td>150 cm males 140 cm females</td>
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<tr>
<td></td>
<td>MOPD II</td>
<td>1000 gm 35 cm</td>
<td>100 cm Worst!!</td>
</tr>
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RUSSELL-SILVER/SILVER-RUSSELL PHENOTYPE

Silver et al 1953, Russell 1954 (no asymmetry)

- Small body compared to head; head is normal for age; and therefore, big relative to body
- Pseudohydrocephaly, "macrocephaly"
- Relatively underweight
- Asymmetry ~ 50% (hemihypotrophy)
- Delayed bone age, but grow parallel to 3rd centile
RUSSELL-SILVER/SILVER-RUSSELL
PHENOTYPE - 2
OFTEN PRESENT

- High forehead
- Triangular shaped face
- Clinodactyly
- Café au lait spots
- Special education needs 35%
Syndactyly 20%
- Hypoglycemia (45% of non UPD)
- Excessive sweating, tachycardia
- Congenital dislocated hip 12%
- Hypospadias, cryptorchidism in 20% males
- Scoliosis 36%
- Bluish sclerae
- Apparently low set ears

HETEROGENEITY

OCCASSIONAL - ? REFLECT
WEIGHT < HEIGHT < OFC

- Programming
- Nutrition
- Fetal survival
  - Placental deficiency/insufficiency
  - Placental (CPM) mosaicism
- Imprinting/epigenetic
- **Chromosome 7**
  - Mat UPD 7 10%
  - 7p11.2-13 mat dUp and other 1%
  - 7q11q1-p14 translocations (x 11)
  - 7q25 translocation
  - Pat 7q32 disruptions
  - Mat 7q32 UPD
- **Trisomy 7 mosaicism**
- **11p15 demethylation**
  - Mat duplication
  - Opposite of BWS 30%
- **15q26.1 – qter deletions**
  - Rings
- **17q22-q24, pat deletion** 2%
- **17q25** 1x
- **AR, AD families**
- **Chromosome 8, 15, 17, 18**
- **Discordant MZ twins**
  - ? All 11p15? 50%
- **Unknown** 50%
WHAT WE HAVE LEARNED ABOUT IMPRINTING?

- Deletion
- UPD (milder)
- Point mutation
- Duplications
- Imprinting control center change
- Methylation changes (LOI)
- Tissue specific expression
<table>
<thead>
<tr>
<th>RS/SR</th>
<th>Imprinted genes normal expression</th>
<th>Disruption</th>
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<tr>
<td>UPD mat</td>
<td>FOX2 pat</td>
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<tr>
<td>p11.1-p14</td>
<td>FOX2 pat</td>
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<tr>
<td>Mat UPD (?1GFBP1↑)</td>
<td>GRB10 pat</td>
<td>(C7oef10-11) ↓</td>
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<tr>
<td>Pericentric inversion</td>
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<tr>
<td>Point mutation</td>
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<td>q32</td>
<td>PEG/MIST mat</td>
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<tr>
<td>Mat dup and UPD</td>
<td>PEG/MIST</td>
<td>(CoPg2 Copg2AS, and MITI, IMP3?) --</td>
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<tr>
<td>11p15</td>
<td>H19 mat</td>
<td></td>
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<tr>
<td>Mat dysfunction</td>
<td>H19</td>
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<tr>
<td>Mat UPD</td>
<td>H19</td>
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<tr>
<td>Loss of paternal methylation DMR</td>
<td>H19 ↑</td>
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<tr>
<td>15q26.1-qter</td>
<td>IGFIR ?</td>
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<td>17q23.3-q25</td>
<td>CHS1 ?</td>
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<td>KPN2</td>
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<td>GRB2 and 7</td>
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CHROMOSOME 7

- **Mat UPD 7**
  - Special education 5%-10%
  - Speech delay (absence of FOXP₂)
  - Fewer minor dysmorphic features
  - No asymmetry
  - Recessive disorders
  - Mat iso 3:5 hetero

- **7p11.2-p14** – mat duplication (GRB10 paternally imprinted – point mutations)
  - (3 AD families)
  - TX and pericentric

- **7q mat UPD 13** – qter (PEG1/MEST maternally imprinted)

- **7q32 translocation breakpoint and δ2-COP**

- **Trisomy 7 rescue with residual T₇ cells**
Demethylation of ICR and pat H19
- regulation of IGF2 expression, biallelic
- expression of H19 – with hypomethylation H19

Opposite of BWS

Asymmetry frequent (fibroblast studies important)

? Cancer risk (small)

Mat duplication 11p15 (35% of the 40%) also UPD

Discordant MZ twins
CHROMOSOME 15

15q26.1-qter deletions and rings apparently loss of functional IGF1R
CHROMOSOME 17

- 17q24.1-q25 translocations, 2% deletions
  - Apparently pat CSH1 expression lost
RS/S/R PRACTICAL ASPECTS

- Early feeding problems
- Hypoglycemia
- ? GH therapy, androgenic hormone
- Leg lengthening discrepancy (> 3 cm)
- Cryptorchidism for males
- Speech/language development
- Hundreds of cases reported
- Very rarely familial
RUSSELL-SILVER/SILVER-RUSSELL
DIFFERENTIAL DIAGNOSIS

- DNA repair
  - Fanconi anemia
  - Nijmegen breakage
  - Bloom syndrome

- Partington
  - X-linked with hyperpigmental skin

- 3-M syndrome

- Fetal alcohol syndrome

- IMAGe syndrome

- Chromosomal
  - Diploid/triploid mixoploidy
  - Mosaic Turner syndrome
  - Y q deletions
  - Trisomy 18 and 18p -
RUSSELL-SILVER/SILVER-RUSSELL REFERENCES

- Hannula K et al. Do patients with maternal uniparental disomy for chromosome 7 have a distinct mild Silver-Russell phenotype?. J Med Genet 2001;38:273-278.
MULIBREY NANISM

**Muscle** **Liver** **Brain** **Eye**
Perhentupa et al 1970 - Finnish

- Large dolicocephalic cranium with high prominent forehead
- Triangular shaped face
- Depressed bridge of nose 90%
- Muscle wasting
- Hands & feet appear large
- Yellowing of retina with yellow spots 80%
- Constrictive pericarditis 35% - (congestive heart failure)
- Enlarged liver with prominent veins 45%
- Long shallow sella turcica (J shaped)
MULIBREY NANISM- 2

- Hypotonia 70 %
- Thin long bones with narrow medullary canal 100%
- Fibrous dysplasia of tibia 25%
- High pitched voice 96%
- Nevus flammeus 65%
- Ovarian stromal tumors
- Wilms tumor 4%
- Incomplete breast development in females
- Premature ovarian failure & subsequent infertility in females
MULIBREY NANISM- 3

- Autosomal recessive – with consanguinity
- Over 80 reported cases
- Finland (85%) and Egypt, France, Turkey, Argentina, Spain
- Mutations occur in TRIM 37 – 17q21 - q24
  - Encodes peroxisomal protein whose function is unknown – it shows a granular cytoplasmic pattern in cells
    - It is a RING – B – box-wild-coil protein
    - Ubiquitin E3 ligase
Feeding problems early
Pericardiectomy often necessary
GH therapy little increase in ultimate weight
Females have spontaneous puberty, then ovarian failure, oligomenorrhea, and infertility
MULIBREY NANISM- 5
DIFFERENTIAL DIAGNOSIS

- Russell-Silver syndrome
- 3-M syndrome
- Meier Gorlin syndrome
REFERENCES

Miller _McKusick_ Malvaux et al. 1975

- Relatively large head, dolicocephaly, with frontal bossing, 50\textsuperscript{th} centile for age
- Short broad neck with prominent trapezius, square shoulders
- Deformed sternum, short thorax
- Transverse grooves on anterior chest, flaring of bottom of chest, transverse ribs
- Square shoulders with winged scapulae
- Triangular face, hypoplastic midface, long philtrum, prominent lips, "gloomy facies"
3 – M – (2)

- Full eyebrows
- Prominent ears
- Fleshy nose tip
- Crowded teeth, V-shaped dental arch
- Short fifth finger
- Hypospadias and hypogonadism in males
3 – M – (3)
Miller McKusick Malvaux et al. 1975

- Hyperlordosis
- Loose joints
- Slender long bone with diaphyseal constriction and flared metaphyses
- Tall vertebrae
- Thoracic kyphoscoliosis
- ? CNS aneurysms
3 – M – (4)
TREATMENT

- Feeding problems
- Male cryptorchidism, infertility
- Watch for kyphoscoliosis
Autosomal recessive, increased consanguinity

Heterozygotes may have minor clinical features

About 100 cases reported

Cullin 7 gene, 25 different mutations in 29 families

CUL7 assembles an E3 ubiquitin ligase complex
DIFFERENTIAL DIAGNOSIS

- Russell-Silver syndrome
- Bloom syndrome
- Mulibrey Nanism
REFERENCES

SHORT SYNDROME
(Gorlin et al and Sensenbrenner et al, 1975)

- Short stature
- Hyperextensible joints/inguinal hernia
- Ocular depression (deep set, large appearing eyes)
- Rieger anomaly (megalocornea, anterior segment dystrophy, glaucoma, and lens opacities)
- Teething delay (small teeth, enamel hypoplasia, malocclusion)
SHORT SYNDROME - 2

- Speech delay (36 months) with normal intelligence
- Triangular shaped face
  - Broad forehead, small chin, small facial bones
  - Telecanthus, deep set eyes, Reiger anomaly
  - Hypoplastic alae, broad nasal bridge
- Micrognathia, dimple in chin
- Dental eruption delay and bone age delay
Feeding problems (V & D) and FTT

Decreased subcutaneous fat, lipodystrophy – dystrophy of face & upper limbs and subcutaneous pits in elbows, and buttocks

DM related to insulin resistance after puberty & GH RX

Thin hair & skin transparent

Occasional neurosensory deafness

Ears – relatively larger, parallel creases, apparently posterior angle
SHORT SYNDROME - 4

- Hyperextensible hands
- Clinodactyly 5th
- Large & cone shaped epiphyses
- Thin, gracile, long bones
SHORT SYNDROME - 5

- 20 cases
- ? 2 AR families; ?4 AD with non penetrance
- Equal males and females
- Translocation 1q31.2/4q25, ? PITX2 mutation
SHORT SYNDROME – 6
DIFFERENTIAL DIAGNOSIS

- GMS
- DeHawere syndrome
- Russell-Silver syndrome
- Polycystic ovary disease


FLOATING HARBOR SYNDROME

Boston Floating Hospital – Harbor General Hospital

(Pelletier et al 1973, Leisti et al 1974)

- Developmental delay, particularly speech 100%
  - Mild MR, some with hyperactivity
- Craniofacial – triangular face (round in infancy)
  - Broad nose, bulbous with prominent nasal bridge
  - Prominent eyes early, deep set later
  - Wide mouth, thin lips
  - Broad columella
  - Smooth and short philtrum
  - Large nares, hypoplastic alae
  - Posteriorly rotated ears, appear lowset
- Head circumference normal for age
FLOATING HARBOR SYNDROME - 2

- Clinodactyly of 5th (nail hypoplasia), brachydactyly, broad thumbs,
- Appear proportionate
- Decreased subcutaneous tissue
- Short neck, with low hairline
- Hirsuitism and long eye lashes
- Joint laxity – 50%
- Trigonencephaly
- Celiac disease
- Occasional high pitched voice
- Tethered cord x1
FLOATING HARBOR SYNDROME - 3

- Delayed BA 100% - but puberty on time
- Clinodactyly of 5th in 75% and coned epiphyses
- Brachydactyly 50%
- Finger clubbed 45%
- Pseudoarthrosis of clavicle
FLOATING HARBOR SYNDROME – 4

- About 20 cases
- Mostly sporadic M:F – 1:2
- Consanguinity, 1 set of female sibs
- Advanced paternal age in most
- x 3 mother daughter affected – doubtful
- Gene Unknown
FLOATING HARBOR SYNDROME – 5
DIFFERENTIAL DIAGNOSIS

- Silver – Russell syndrome
- Shprintzen syndrome
- 3-M syndrome
- Dubowitz syndrome
- Rubinstein – Taybi syndrome
REFERENCES


BLOOM SYNDROME
(Bloom 1954, German F/U)

- Microcephaly – mildly/small for size
- Malar mynoplasia
- Telangiectasia and erythema of face (butterfly distribution)
- Pigment abnormalities and atrophic scars (photosensitivity by 2 years)
- Increased risk of tumors: leukemia, lymphoma, adenocarcinoma, squamous cell, carcinoma, and Wilm’s (at least 44% affected, mean age of onset 25 years)
BLOOM SYNDROME – 2

- High squeaky voice
- Immune deficiency and reduced 1gA, 1gG, 1gM
- Chronic infections (particularly chronic lungs 20%)
- Male infertility with small testes, females fertile with premature menopause
BLOOM SYNDROME - 3

- Delayed puberty (and BA)
- DM 16% - type 2 after puberty
- Mild MR – normal IQ with learning disability
- Feeding problems in infancy
- Male infertility with small testes, females fertile with early menopause
Increase sister chromatid exchange (SCE) breakage, dicenrics, tetraradials
Autosomal recessive

Mutations in BML (15q26.1) which is a protein homologous to REC Q helicase

64 mutations, 2 Ashkenazi mutations

Ashkenazi Jew carrier rate about 1%

Unwinds DNA in 3’ to 5’ direction along bound strand, nuclear cell cycle regulator

Other DNA helicase disorders - Werner, Rothman Thompson
Bloom syndrome registry ~ 150 patients maintained by German & Passarge

- Helps to clarify the natural history
BLOOM SYNDROME - 7
DIFFERENTIAL DIAGNOSIS

- Russell Silver syndrome
- Rothmund Thompson syndrome
- Cockayne syndrome
- Ataxia Telangiectasia
- Fanconi Anemia


DUBOWITZ SYNDROME - 1
Dubowitz 1965

- DD & MR – mild – moderate (72%)
- Hyperactivity 70%
- Shy, short attention span
- Speech delay 67%
- High pitched voice 55%, hoarse cry 30%
- Microcephaly, high sloping forehead 80%, flat superorbital ridges 90%, present at birth
- Exzema – like skin disorder on face & flexion areas, 60% from birth, clears 2 – 4 years
- Space hair, especially frontal 70% and lateral eyebrows 45%
DOBOWITZ SYNDROME – 2

- FTT - Muscular hypotonia 40%
- Delayed BA 50%
- Faces become triangular
- Broad nasal tip 50% and broad base to nose
- Telecanthus with prominent epicanthal folds, ptosis 65%, blepharophimosis 80%
- Apparently low set, prominent, dysmorphic ears 75%
DOBOWITZ SYNDROME – 3

- Small chin 80%, with age becomes long square chin
- Clinodactyly of fifth - 50% and syndactyly 20%
- Males hypospadias, cryptorchidism 50%
- Leukemia, lymphoma, neuroblastoma, and aplastic anemia have been reported
DOBOWITZ SYNDROME – 4

- 150 cases
- AR many with consanguinity
- ? Subtypes
  - ? Anorectal & craniosynostosis subtypes
  - Immune deficiency and frequent infection
  - Low cholesterol
- Gene unknown
DOBOWITZ SYNDROMES – 5
DIFFERENTIAL DIAGNOSIS

- FAS syndrome
- Bloom syndrome
- Smith-Lemli-Opitz syndrome
- 22q- syndrome


MAJEWSKI (MICROCEPHALIC)
OSTEODYSPPLASTIC PRIMORDIAL
DWARFISM II
Majewski et al 1982

- Severe IUGR < 1000 gm at term
- Severe postnatal short stature – around 100 cm as adult
- At birth, proportionate OFC (28 weeks at term)
- Progressive relative true microcephaly
- Forehead lacks posterior slant, in fact tall, forehead
- Small dysplastic teeth (or absent) compared to mouth size
- High squeaky voice
- Prominent nose and eyes
MOPD II - 2

- Progressive bony changes and loose jointedness with disproportionate shortening of mesomelic segment
- Brachydactyly
- Bowed legs
- Develop café au lait spots
- May have depigmentation spots
- Develop dark pigment with some acanthesis around neck & axilla
- Far sighted, short globe
- Pleasant personality
MOPD II - 3

- Develop intracranial aneurysm
- Develop truncal obesity
- Rarely DM
- Cutis marmorata seen
- Males cryptorchidism, hypospadias, micropenis
- Reduced life expectancy – oldest 40 years old
- No increase in cancer noted
MOPD II – 4
MANAGEMENT

- Feeding problems
- Little or no response to GH
- Scoliosis may develop
- CNS aneurysm need to be screened for
- Avoid sun
- Watch for dislocation radius & knees
- Danger from being so small
- Watch for DM
MOPD II - 5

- Autosomal recessive with consanguinity
- Increase among Mediterranean countries
- Variability in same family
- About 100 cases reported
Percentrin (PCNT) mutations
Component of centrosome complex
Role in cell division (mitosis)
Helps to organize mitotic spindle for segregation and anchoring of spindle
Giant coiled coil protein localized to centrosome throughout cell cycle
21q22.3
MOPD II - 7

- Meier-Gorlin syndrome
- Floating Harbor syndrome
- 3 – M syndrome
- SHORT syndrome
- Seckels syndrome
- MOPD I and III


SUMMARY 1
ALL PROPORTIONATE, IUGR, AND POST-NATAL SHORT STATURE

- Bloom syndrome
  - Mild microcephaly, malar hypoplasia
  - Telangectasia erythemations rash on cheeks and with sun exposure

- Floating Harbor syndrome
  - Speech delay - mild MR
  - Changing face – prominent nose, short philtrum
  - BA delay, but puberty on time

- SHORT
  - Riegers (lens opacity, glaucoma), eyes large appearing, then deepset
  - Lipodystrophy of face and upper torso
  - Speech delay – IQ okay
  - Hypoplastic alae, prominent nose as adults
SUMMARY 2
ALL PROPORTIONATE, IUGR, AND POST-NATAL SHORT STATURE

- Dubowitz syndrome
  - Relative microcephaly
  - Eczema
  - Sparse lateral eyebrows
  - Telecanthus, prominent epicanthal folds

- Russell-Silver/Silver-Russell
  - Normal size head (pseudohydrocephaly)
  - Relatively underweight
  - 50% asymmetric
  - BA delay, late puberty

- Mulibrey Nanism
  - Large, long head with triangular face with depressed bridge of nose
  - Constructive pericarditis and heart failure with liver enlargement
  - Yellow pigment and spots in retina
  - Fibrosis of ovaries, fibrodysplasia of tibia
SUMMARY 3
ALL PROPORTIONATE, IUGR, AND POST-NATAL SHORT STATURE

- **3-M**
  - Short thorax with sternal deformity, transverse ribs, rib groove
  - Broad neck, square shoulders, prominent trapezius
  - Triangular face, full lips, hypoplastic midface, long philtrum

- **MOPD II**
  - Severe pre & postnatal growth
  - Progressive microcephaly, high forehead
  - Prominent nose, small teeth, squeaky voice
  - Progressive boney dysplasia
SEVERE IUGR

- Epigenetic control of growth
- Ubiquinoation
- Peroxisomal function
- Centrosomal function – mitotic spindle
- DNA repair

- Chromosomal aberrations
- Teratogens
- Placental function
COMMON AND OVERLAPPING FEATURES

- Large appearing head
- Triangular shaped face
- Decreased subcutaneous fat
- Delayed bone age
- Feeding difficulties as an infant
- High pitched voice
- Infertility
- Clinodactyly of the fifth finger
- Pigment abnormalities
- Bone changes of disuse (tall vertebrae, dolicocephaly, thin ribs, and long bones)
“A” LIST

1. Bloom*
2. Dubowitz
3. Floating Harbor
4. MOPD II*
5. Mulibrey*
6. Silver-Russell/Russell-Silver***
7. SHORT
8. 3-M*

Also: Chromosomal, CPM, and teratogens
“B” LIST

Gorlin/Smith/Jones
- Aarskog Sx
- de Lange Sx
- Hallerman Streiff Sx
- Meire-gorlin Sx
- Rubinstein Taybi Sx
- Seckel’s Sx

Hall 2004 article on MOPD II
- Toriello 1986
- Saul Wilson Hersh 1990 & 1994
- Hurst 1988
- Sdfs
- Bluebel 1996
- Cervenka 1979
- Frias 2005
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