KNOW WHAT IS NOT RIGHT: RECOGNIZING DYSMORPHIC FEATURES AND WHAT THEY COULD MEAN!
WHAT YOU MAY SEE IN YOUR PEDIATRIC CLINIC . . .
May be seen in children with or without associated syndromes
SYNDROMES ASSOCIATED WITH SYNOPHRYS

- Cornelia de Lange Syndrome
- Fetal Trimethadione Syndrome
- Sanfilippo Syndrome
- Waardenburg Syndrome
- Others:
  - Deletion 3p Syndrome
  - Deletion 9p Syndrome
  - Duplication 3q Syndrome
  - Duplication 4p Syndrome
CORNELIA DE LANGE SYNDROME
AKA BRACHMAN DE LANGE SYNDROME

- 1 in 10,000 live births
- Clinical diagnosis
  - 3 known mutations
- Low birth weight, short stature, microcephaly
- Developmental delay
- GERD
- Behavioral issues
  - self-injury
  - autistic-like behavior
  - anxiety
  - OCD
  - ADHD
- Facial features
  - synophrys
  - Short upturned nose
  - thin downturned lips
  - low-set ears
  - high-arched/cleft palate
- Limb anomalies
CORNELIA DE LANGE SYNDROME - MANAGEMENT

- At time of diagnosis:
  - Karyotype (typically normal)
  - Echocardiogram
  - Renal ultrasound
  - Ophthalmology referral
  - Hearing evaluation
  - Upper GI (R/O malrotation or reflux)
  - Evaluate for GERD
  - Developmental assessment (special development chart)
  - Early intervention services
  - Special growth charts, high calorie formulas
  - Support organization information for the family
  - Genetics counseling
- Later: behavioral or psychiatric assessment
- At risk for volvulus, malrotation, and GI necrosis
FETAL TRIMETHADIONE SYNDROME

- Trimethadione is a teratogenic anticonvulsant
- Rare disease
- High fetal loss rate
- Craniofacial features
  - microcephaly
  - flat midface
  - synophrys, v-shaped eyebrows
  - short nose
- Cardiac anomalies
- Absent kidney and ureter
- Meningocele
- Omphalocele
- Developmental delay
SANFILIPPO SYNDROME
AKA MUCOPOLYSACCHARIDOSIS III

- Autosomal recessive lysosomal storage disease
- 1 in 24,000 live births
- Normal development until age 2, then progressive neurologic impairment, life expectancy 12-20
- Gene therapy trial in progress
WAARDBERG SYNDROME

- Autosomal dominant
- Abnormal melanocyte distribution in embryogenesis
- 4 types
  - Type 1&2 – more common
  - Type 2 – more likely to be deaf
  - Type 4 - Hirschsprung
- Major criteria:
  - Sensorineural hearing loss
    - Congenital deafness in 20%
  - Iris pigmentary anomalies
  - Hair hypopigmentation
  - Dystopia canthorum
  - 1st degree relative
- Minor criteria:
  - skin hypopigmentation
  - synophrys
  - broad nasal root
  - hypoplasia alae nasi
  - premature graying
HEMIHYPERTROPHY
- Beckwith-Wiedeman Syndrome
- Russell-Silver Syndrome
- Proteus Syndrome
- Poland Anomaly
- Klippel-Trenaunay Syndrome
BECKWITH WIEDEMAN SYNDROME

- Gene map locus 11p15
- Characteristics: macrosomia, macroglossia, prominent eyes with infraorbital hypoplasia, ear creases, umbilical hernia/omphalocele
- Hypoglycemia in early infancy due to pancreatic hyperplasia, neonatal polycythemia, organomegaly (liver, kidney, adrenal, pancreas)
Special feeding techniques or speech therapy due to the macroglossia.

Surgical intervention for abdominal wall defects, leg length discrepancies, and renal malformations.

Increased risk for tumor formation!!

7.5%, further increased to 10% if hemihyperplasia is present

Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma

Important Screening Measures:
(1) Abdominal US q3 months until 8 years old
(2) Serum alpha-fetoprotein q6 weeks as a screen for hepatoblastoma until 3 years old

Interesting Fact: ART used 10-20xs more in BWS infants, risk after IVF 1 in 4000 (9 fold higher than general population)
Russell Silver Syndrome

Characteristics:
- short stature
- triangular facies
- prominent forehead
- narrow chin
- small jaw
- down-turned corners of the mouth
- café-au-lait spots
- clinodactyly
- excess sweating
- asymmetry of limbs
RUSSELL SILVER SYNDROME

- Intrauterine growth retardation, postnatal growth retardation, normal head circumference
- Liability to fasting hypoglycemia from 1-3 yo
- Digestive system abnormalities
- Associated with an increased risk of delayed development and learning disabilities.
PROTEUS SYNDROME

- rare (only a few hundred worldwide)
- mosaic mutation in a gene ‘AKT1’
- asymmetric overgrowth of the extremities
- generalized thickness of skin and subcutaneous tissue (muscles and bones)
- pigmented epidermal nevi
- hamartomatous tumors
- macrodactyly
- hemihypertrophy
- syndromic hemimegalencephaly
- severe seizures, beginning in neonates, (uncommon)
### General Criteria
- Mosaic Distribution
- Progressive Course
- Sporadic Occurrence

### Specific Criteria

**Category A**
- Cerebriform connective tissue nevus

**Category B**
- Linear epidermal nevus
- Asymmetric, disproportionate overgrowth of two of:
  - Limbs, skull, external auditory canal, vertebrae, or viscera
- Specific tumors in the first decade of life:
  - Bilateral ovarian cystadenomas
  - Monomorphic parotid adenomas

**Category C**
- Dysregulated adipose tissue
- Vascular Malformations
  - Capillary, venous, and/or lymphatic
- Lung bullae
- Facial phenotype:
  - Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest

The diagnosis of Proteus syndrome requires all three general criteria, plus one criterion from category A, or two criteria from category B, or three criteria from category C. (Adapted from Biesecker, 2006)
POLAND ANOMALY

- Unilateral features (75% right-sided)
- Hypoplasia/absence of pectoralis major muscle, nipple, areola
- Short, webbed fingers (symbrachydactyly), oligodactyly of ipsilateral hand
- Possible hemivertebrae, renal anomalies sprengel deformity
- Right > Left, Males > Females
KLIPPEL TRANAUNEY SYNDROME

- 1) cutaneous vascular malformation
- 2) bony and soft tissue hypertrophy
- 3) venous abnormalities

- Present at birth, usually involves lower limb
- Capillary malformation localized to hypertrophied area
- Deep venous system absent or hypoplastic
- Thick-walled venous vasicosities ipsilateral to vascular malformation apparent after child begins to ambulate
- If associated AVM: KT – Weber Syndrome
Pain, limb swelling, cellulitis can occur
Less frequently: thrombophlebitis, dislocation of joints, gangrene of affected extremity, heart failure, hematuria 2/2 to angiomatous involvement of urinary tract, rectal bleeding from lesions of GI tract, pulmonary lesions, malformation of lymphatic vessels
Imaging: arteriograms, venograms, CT/MRI to determine extent of anomaly
Surgical correction/palliation often difficult
Doppler US guided percutaenous sclerotherapy can be helpful
Supportive care: compression bandages for varicosities, orthotic devices for leg-length discrepancies
DOWNTURNED CORNERS OF THE MOUTH

- Cornelia de Lange Syndrome
- Escobar Syndrome
- Robinow Syndrome
- Russel-Silver Syndrome
- Others
  - Deletion 3p Syndrome
  - Deletion 4p Syndrome
  - Deletion 18p Syndrome
  - Deletion 18q Syndrome
ESCOBAR SYNDROME

- Autosomal recessive
- Dysfunction of acetylcholine receptor fetal gamma subunit
- Congenital arthrogryposis
- Pterygia (webbing) of neck, elbows, knees, axilla
- Respiratory distress
ROBINOW SYNDROME

- ~100 cases described
- "Fetal facies", small face, widely-spaced eyes
- Tented upper lip, dental crowding, gum hypertrophy
- Short-extremity dwarfism
- Vertebral and genital anomalies
- Autosomal dominant and autosomal recessive forms

*Fig. 1 - 9 year old boy with short limbs, typical facies and limited extension of the elbows and knees.*
CRANIOSYNOSTOSIS

- Occurs in 1:1500 to 1:1900 live births
- Isolated nonsyndromic sagittal synostosis most common

Sagittal Synostosis = Scaphocephaly
Metopic Synostosis = Trigonocephaly
WHAT TO LOOK OUT FOR

- Nonsyndromic, simple craniosynostosis vs. Syndromic Complex Craniosynostosis
- If >one suture $\rightarrow$ more rare, AD pattern
- Syndromes to Consider:
  1) Apert
  2) Crouzon
  3) Pfeiffer
COMPLEX CRANIOSYNOSTOSIS

- Genetics --> mutations that result in patterns of suture fusion and systemic anomalies assoc. w/ >100 syndromic craniosynostosis
- Fibroblast Growth Factor Receptors (FGFR) responsible for restraining growth → various mutations in its gene associated with craniosynostotic syndromes

<table>
<thead>
<tr>
<th>GENE/PROTEIN</th>
<th>SYNDROME</th>
<th>CHROMOSOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>Pfeiffer</td>
<td>8</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Apert</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Crouzon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pfeiffer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jackson-Weiss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beare-Stevenson</td>
<td></td>
</tr>
<tr>
<td>FGFR3</td>
<td>Muenke</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Crouzon with AN</td>
<td></td>
</tr>
</tbody>
</table>
APERT SYNDROME

- AD with incomplete penetrance, majority new mutations
- 1) Craniofacial: coronal synostosis → bracycephaly and high cranium, full forehead with flat occiput, flat facies, shallow orbits, hypertelorism, small nose
- Limb anomalies: dyymmetric syndactyly, short fingers
APERT SYNDROME: FEATURES AND FINDINGS

Craniofacial
- Brachycephaly due to coronal suture synostosis
- Hypertelorism
- Proptosis
- V-pattern exotropia
- Midface hypoplasia
- Choanal stenosis
- Cleft palate
- Stylohyoid calcification
- Conductive hearing deficits

Extracranial Skeletal
- Symmetrical syndactyly of the hands
- Cervical spine fusion
- Shortened humeri

Other
- Cardiovascular anomalies
- Hydronephrosis
- Cryptorchidism
- Tracheal anomalies
- Obstructive sleep apnea
- Diffuse acne

![Images of APERT Syndrome features](A, B, C, D)
WHAT TO CONSIDER

- significant eye injury (proptosis and exotropic)
- Strabismus → visual acuity problems
- More frequent middle ear infections
- Various intracranial anomalies (early baseline MRI, baseline CT scan and serial exams to eval intracranial htn)
- Developmental delays/cognitive deficits
- Correction of coronal sutures (age of operation affects intelligence)
CROUZON SYNDROME

- AD with variable expression; 60% new mutations
- Characteristics: ocular proptosis due to shallow orbits, hypertelorism, frontal bossing, maxillary hypoplasia, hearing loss, brachycephaly due to bilateral coronal craniosynostosis, bifid uvula, +/- cleft palate
WHAT TO CONSIDER

- Chiari I malformations present in 71% of cases (assoc with hindbrain herniation in small %) → due to early closure of lambdoid sutures
- Early MRI to eval hydrocephalus and provide baseline imaging
- Conductive hearing loss due to midface anomalies
- Possible neurosensory hearing loss
- Frequent OM due to impeded eustachian tube function
- Hearing evaluation and serial monitoring, ENT involvement

CROUZON SYNDROME: FEATURES AND FINDINGS
Craniofacial
Brachycephaly due to coronal suture synostosis
Hydrocephaly with Chiari I malformation
Hypertelorism
Proptosis
Midface hypoplasia
“Beaked” nose

Cleft palate
Stylohyoid calcification
Conductive and/or neurosensory hearing deficit
Extracranial Skeletal
Cervical spine fusion
Other
Acanthosis nigricans
PFEIFFER SYNDROME

- Characteristics: brachycephaly with craniosynostosis of coronal, with or without sagittal sutures; full high forehead, ocular hypertelorism, shallow orbits, proptosis, broad thumbs and toes, hearing loss (secondary to anatomic abnormalities)
- Etiology: autosomal dominant or sporadic; three types, type 2 associated with cloverleaf skull
- 3 clinical subtypes: Type I – normal intelligence, good prognosis, Types II and III – mental retardation, poor prognosis
- strabismus
- Frequent OM
- Conductive hearing loss due to midface anomalies
- Hearing Eval and ENT involvement
- Visceral GI manifestations less common (pyloric stenosis, malpositioned anus)
## Pfeiffer Syndrome: Features and Findings

### Craniofacial
- Acrocephaly, or turribrachycephaly (oxycephaly,) due to coronal suture synostosis
- Kleeblattschädel sutural deformity
- Hydrocephaly
- Midface hypoplasia
- “Beaked” nose
- Hypertelorism
- Proptosis
- Blindness
- Choanal atresia
- Mental retardation

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrocephaly</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleeblattschädel</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Midface hypoplasia</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>“Beaked” nose</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Proptosis</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Blindness</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Choanal atresia</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

### Extracranial Skeletal
- Broad, radially deviated thumbs
- Broad, medially deviated great toes
- Soft-tissue syndactyly
- Elbow ankylosis

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad, radially</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Broad, medially</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Soft-tissue syndacty</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Elbow ankylosis</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
BLUE SCLERAE

- Osteogenesis Imperfecta Types 1 and 2
- Marshall-Smith Syndrome
- Roberts-SC Phocomelia
- Russel-Silver Syndrome
OSTEOGENESIS IMPERFECTA

- Autosomal dominant or recessive mutation in collagen-coding gene
- Multiple types
  - Type 1 is mildest and most common form (50%) – may have few symptoms
  - Type 2 (OI congenita) - most severe, cardiac defects, death in neonatal period
  - Type 3 (severe OI) – often wheelchair bound
  - Type 4 (moderately severe OI) - may need braces or crutches
- Manifestations
  - Blue sclera
  - Multiple fractures
  - Hearing loss
  - Joint hypermobility
  - Scoliosis, deformities
- Diagnosis: skin punch biopsy
- Treatment
  - Bisphosphonates
  - Growth hormone
  - Low impact exercise
  - Bracing or surgery
  - Support for body image concerns
  - Genetic counseling
ROBERTS-SC PHOCOMELIA SYNDROME
AKA PSEUDOTHALIDOMIDE SYNDROME

- ~150 reported cases
- Autosomal recessive tetraphocomelia
- Premature centromere separation
- Marked variability in expression
- Craniofacial anomalies (e.g. cleft lip/palate)
- Nose and ear anomalies
- Severe intellectual disability
- Clinical and cytogenetic diagnosis
MARSHALL-SMITH SYNDROME

- Very rare
- Advanced bone age at birth
- Wide prominent forehead
- Prominent eyes
- Micrognathia
- Upturned nose
- Laryngeotracheal anomalies
- Feeding difficulties
- Developmental delay
ADDITIONAL RESOURCES

- POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)
- LDDDB (London Dysmorphology Database)
- SYNDROC (Syndrome Congenital Malformation Database)
RESOURCES