TUTORIAL 5

DYSMORPHOLOGY

Dysmorphology is the branch of clinical genetics in which clinicians and researchers study and attempt to interprete the patterns of human growth and structural defetcs.

OVERALL OBJECTIVES

At the end of this module the student should be able to:

- Recognise major malformations and describe dysmorphic features
- Interprete the patterns of human growth and structural defects
- To reach an acceptable diagnosis for chidren with dysmorphic features and describe this in keeping with a particular
    - Syndrome
    - Sequence
    - Association

In order to start examination of a child with dysmorphic features you need to have relevevant family history and ages of both parents.

Expose the child in steps as you go along the clinical examination and inspect:

CRANIOFACIAL

Head

- Hair: quality, texture, distribution
- Shape: symmetrical or asymmetrical
- OFC: normo, macro or micocephalic, brachycephalic
- Is there craniotabes? Painful- be gentle. Not of significance under 3 months

Craniotabes: It is thinning of skull outer table. When pressed firmly over occiput or parietal bones, it gives-way as if pressing on Ping-Pong ball. It can be a normal variant or present in newborns, resolves by 1 month of age or may persist normally at suture lines

Differential Diagnosis includes: Rickets, osteogenesis imperfecta, hydrocephalus.

Fontanelle

- **Anterior:** diamond shaped
- **Posterior:** triangular
- **Third fontanelle:** may only be barely perceptable widening of the sagital suture between anterior and posterior fontanelles. It may be a normal varient or clue to Down syndrome
- **Closed or open:** If open – is it normal, under tension or sunken
- Fontanelles usually close around 1 year of age. Delayed closure > 18 months may suggest:

    - Hydrocephalus
    - Down syndrome
    - Hypothyroidism
- Abnormally wide fontanelle at any age may suggest:
    - Rickets
    - Hypothyroidism
    - Cranial synostosis
    - Rare syndromes like:
        - Smith-Lemli-Opitz syndrome
        - Zelweger's syndrome
        - Rubinstein-Taybi syndrome

Sutures: palpate with the finbers and palm of your hand

- Coronal
- Sagital
- Lambdoid
- Metopic: in the midline of the forehead due to early synostosis between the frontal bones (cosmatic problem only)

FACIAL FEATURES

Divide face into 4 regions

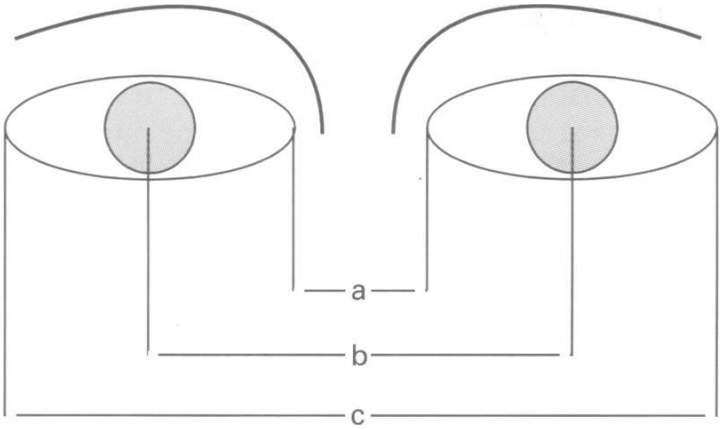
Forehead

- Overt prominance: achondoplasia
- Bitemporal narrowing: high forehead – occasional vertical ridges on forehead → Miller Dieker syndrome
- Sloping appearance - primary microcephaly

Mid face

From eye brows to the upper lip & from outer canthi to the commissures of mouth

- Look at inner canthal distance
- Measure interpupillary distance if suspecting abnormal – ask for charts to plot



- **Check for Hypotelorism**: may be associated with defect in midline brain formation

Hypotelorism is narrowness of the intraorbital distance which may occur as a morphogenetic varient or in association with other anomalies like epicanthic folds (vertical folds of skin on either side of the nose), or secondary to cranial dystrophy.

- **Check for Hypertelorism** (roughly check if 3rd eye can fit in)

Hypertelorism is wide separation of eyes or increased intraorbital distance (> +2 SD). It may be morphogenetic varient, a primary deformity or secondary phenomenon in association with developmental abnormalities like: frontal meningocele, encephalocele and persistance of facial cleft. It may be associated with strabismus, extropia or optic atrophy.

- **Exophthalmos**
  - It is protrusion of eyes commonly due to orbital disease
  - Shallowness of orbits due to craniofacial malformations
  - Increased tissue mass in orbit like neoplasia, vascular, inflammatory disorders

  Occular complications due to exophthalmos include:
    - Exposure keratopathy
    - Occular motor disturbances
    - Optic atrophy – loss of vision
- **Enophthalmos**
  - It is shrinking of the eye back into the orbit that may be due to
    - Orbital fracture
    - Atrophy of orbital tissue
- **Thyroid related ophthalmopathy**
  - It is believed to be secondary to immune mechanisms leading to inflammations and deposition of mucopolysaccharoids and collegen in extraoccular muscles and orbital fat.
  - Involvement of extra occular muscles may lead to restrictive strabismus
  - Complications include corneal exposure leading to inflammation and perforation and compression of optic nerve.
- **If Protuberant upper lip** with thin vermian border, consider Miller Dieker syndrome
- **If short length of pelpebral fissure consider** foetal alcohol syndrome
- If excesive length of pelpebral fissure consider Kabuki make up syndrome (with short stature and mental retardation)

EYES

A direct ophthalmoscopic examination helps assess the status of optic discs and macula. Complete examination of retina requires dilating the pupil and using an indirect ophthalmoscope.

Abnormalities noted

- Coloboma
- Conjunctival telangiectasia
- Upward stant: consider Downs syndrome
- Downwards slant: consider Treacher Collins syndrome

- Prominent epicanthic folds: consider Downs or Foetal alcohol syndrome
- Squint: consider Fanconi's syndrome or 6th nerve palsy with intracranial bleed
- Proptosis: consider Fanconi's syndrome or 3rd nerve palsy or myasthenia gravis
- Synophrys: eyebrows that meet in the midline
- Cataract: consider diabetes mellitus, congenital rubella, galactosaemia

NOSE

- Nasal bridge
  - Flattened: Down or Foetal alcohol syndrome
  - Prominent: Velocardiofacial syndrome

MALAR REGION

It extends from ears to the midline

Note:

- Size and shape
- Low set ears
- Posterior rotation
- Pre-auricular skin tag
- Ear lobe creases (Beckwith-Wiedemann syndrome)
- Note if the child has a hearing aid. Deafness can occure in Treacher Collin, CHARGE, foetal rubella and Waardenburg syndrome

MANDIBULAR REGION

It extends from lower portion of ears bounded out to the chin by the mandible

- Small chin: consider Pierre Robin syndrome

NECK

- Webbing of neck: consider Turner or Noonan syndrome
- Short neck: consder Klippel-Feil syndrome
- Position of posterior hair line is low: consider Klipple-Feil or Noonan syndrome

TRUNK

- Sheild like chest: consdier Turner or Noonan syndrome
- Pectus deformity: consider Marfan syndrome
- Scoliosis: consider Marfan syndrome

EXTREMITIES

- Check knee joints: look for patella (missing patella in "Nail Patella Syndrome")
- Check range of movements of all joints and screen for carrying angle
  - Increased (cubitus valgus)
    - Turner syndrome

        - Noonan syndrome
- Check if joint laxity is present:
    - Hypermobility
        - Osteogenesis imperfacta
        - Marfan syndrome (wrist sign, thumb sign)
        - Ehler-Danlos syndrome
    - Multiple contractures
        - Arthrogryposis multiplex congenita
    - An inability to pronate and supinate elbow
        - radioulner synostosis
            - X chromosome aneuploidy
            - Foetal alcohol syndrome

HANDS

- **Syndactyly:** two or more digits at least partially or completely fused: consider Apert syndrome, Smith-Lemli-Opitz syndrome
- **Polydactyly** (extra digit): consider Ellis-van Creveld syndrome
- **Brachydactyly** (short digits): consider Aarskog syndrome, Downs syndrome
- **Camptodactyly** (digit is bent or fixed in direction of flexion): cab be associated with other skeletal anomalies and number of congenital syndromes like Jacobson syndrome and Beals syndrome.
- **Clinodactyly** (digit is crooked, curves towards or away from the other digits): consider Russell-Silver syndrome

DERMATOGLYPHICS

- Single transverse palmer crease and hypotonia during early foetal life: consider Downs syndrome in 50% cases but can be normal in 10% cases.
- Characteristic palmer pattern is seen in Foetal alcohol syndrome

GENITALIA

- Disorder of sexual differentiation may indicate congenital adrenal hyperplasia
- Hernia; especially in neonate and hypospadias; if associated with cryptorchidism, there is strong possibility of a syndrome

MAKE AN ASSESSMENT

Try to recognize if it is Syndrome, Sequence or Association, otherwise say you don't recognize a particular syndrome but would either refer or try to look it up. Chromosome studies are indicated when 3 or more than 3 dismorphic features are present.

Common Syndromes

Down syndrome

- Trisomy 21: non-dysjunction (95%), translocation (4%), mosaicism (1%)
- Flat facial profile, Up slanting eyes, Epicanthic folds, Flat nasal bridge, Small and low set eras, Protruding tongue
- Short stature, Brachydactyly, 5th finger clinodactyly, Single palmer crease, Sandal-gap between 1st and 2nd toes
- Congenital heart defect (40%), Duodenal atresia, Hypotonia, Brachycephaly
- Complications: Hypothyroidism, Acute leukaemia, Alzheimer's disease, Mental retardation
- Diagnosis: QF-PCR aneuploidy test, Karyotyping
- Treatment: growth and neurodevelopment monitoring**.** Medical treatment of cardiac failure and hypothyroidism, neurodevelopmental interventions
- Prevention: Female education, Family planning, Pregnancy screening for advanced maternal age (AMA), Sonar and maternal screening, Screening for hypothyroidism

Turner syndrome

- Appearance: short neck with a webbed appearance
- Low hairline at the back of the neck
- Low-set ears
- Hands and feet that is swollen or puffy at birth
- Soft nails that turns upward.
- Broad chest with widely spaced nipples
- High, narrow roof of the mouth (palate)
- Arms that turn outward at the elbows
- Fingernails and toenails that are narrow and turned upward
- Swelling of the hands and feet, especially at birth
- Slightly smaller than average height at birth
- Slowed growth
- Cardiac defects
- Receding or small lower jaw
- Short fingers and toes

CATCH 22

- **C**ardiac defects – Interrupted aortic arch, truncus arteriosus, VSD, PDA, TOF
- **A**bnormal facial features – wide set eyes, narrow small groove in upper lip, small jaw
- **T**hymus underdevelopment
- **C**left palate
- **H**ypercalcaemia

CHARGE association

- **C**oloboma and cranial nerve abnormalities – defects of the eye ball
- **H**eart anomalies – TOF
- **A**tresia of choanae – bony and or membranous
- **R**etardation of growth – both cognitive and somatic growth
- **G**enital anomalies and or hypoplasia in males

- **E**ar anomalies and or deafness

CHILD syndrome

- **C**ongenital **H**emidysplasia
- **I**chthyosiform erythroderma
- **L**imb **D**efects

LEOPARD syndrome

- **L**entigines (brownish pigmented spots on skin due to increased deposition of melanin & increased number of melanocytes)
- **E**CG abnormalities: axis deviation, unilateral or bilateral ventricular hypertrophy, conduction abnormalities
- **O**cular hypertelorism
- **P**ulmonary stenosis
- **A**bnormal genitalia
- **R**etardation of growth, deafness

PHASE Syndrome *(Frieden et al 1996 – Neuron 2011)*

- **P**osterior fossa anomalies
- **H**aemangioma
- **A**rterial lesions
- **C**ardiac abnormalities – aortic co-arctation
- **E**ye abnormalities

VACTERL / VATER association

- **V**ertebral anomalies
- **A**nal atresia with or without fistula
- **C**ardiac anomalies – VSD
- **T**racheo-**E**sophageal fistula with oesophageal atresia
- **R**enal anomalies – urethral atresia, with hydronephrosis
- **L**imb anomalies – polydactyly, humeral hypoplasia, radial aplasia and proximally placed thumb

CRANIOSYNOSTOSIS *(Nelson p2456)*

- Premature closure of cranial sutures
- **Primary** – closure of one or more sutures due to abnormality of skull development
- **Secondary** – due to failure of brain growth

Crouzen Syndrome (Ziai page 21)

- Craniofacial dysostosis, Shape of head depends upon timing, often is compressed back to front diameter, Orbits are underdeveloped & Ocular proptosis is prominent
- Hypoplasia of maxilla & orbital hypertelorism are typical facial features
- Beak type nose, Exophthalmos, Strabismus, Short upper and protruding lower lip

Apert syndrome

- Syndactyly of 2^{nd}, 3^{rd} & 4^{th} fingers which may be joined to thumb & the 5^{th} finger
- Similar abnormalities often occur in feet
- Progressive calcification & fusion of bones of hands, feet and cervical spine
- Mental retardation, Asymmetric facies – eyes are less proptotic than Crouzen

Carpenter Syndrome

- Many fusions of suture, tend to produce the Kleeblattschadel skull deformity
- Soft tissue syndactyly of hands & feet is always present

- Mental retardation, Obesity, Hypogonadism (Ziai page 22)
- Heart disease, Corneal opacities, Coax valga and genu varum

Pfeiffer syndrome

- Commonly associated with turricephaly, Eyes are prominent (widely spaced)
- Thumbs and great toes are short and broad, Partial soft tissue syndactyly

Each of the above genetic syndromes poses additional anomalies including

- Hydrocephalus and increased intracranial pressure
- Optic atrophy – due to abnormalities of optic foramina
- Respiratory problems secondary to a deviated nasal septum or choanal atresia
- Disorders of speech and deafness
- Craniotomy is mandatory for management of increased intracranial pressure

Hunter's Syndrome *(Forfar p983)*

- Usually between 2-5 years but milder types
- Slowly deteriorating MR, Stunted growth – claw hands
- Hepatosplenomegaly & Cardiac defects due to infiltration into valves & arterial walls
- Papilledema (may lead to blindness)
- Hernias, Progressive deafness, Carpel Tunnel Syndrome
- Differs from Hurler's – no gibbous formation

Kabuki Makeup Syndrome

- Mental retardation, Short stature
- Unusual skin ridges patterns on the fingers, toes, palms of hands & soles of feet

Klipple-Feil Syndrome

- Short neck, low hair line, Sensorineural hearing loss
- Paralysis of external rectus muscles – one or both eyes squint

Miller Dieker Syndrome

- Lissencephaly, Sever hypotonia at birth
- Seizures with corticospinal tract signs

Pierre Robin Syndrome *(Nelson p1534)*

- Triad of micrognathia + glossoptosis (results in) → airway obstruction
- Micrognathia is usually associated with high arched palate & cleft palate. Tongue usually of normal size but floor of the mouth foreshortened. Obstruction of air passage may occur, on inspiration – usually requiring treatment to prevent suffocation
- Tracheostomy or endotracheal intubation may be required
- Mandibular distraction procedures in neonates can improve mandibular size – enhance respiration – facilitate oral feeding
- Sufficient mandibular growth may take place to relieve obstruction – growth often achieves normal profile in 4-6 yrs
- Dental anomalies require individual treatment
- 50% of children with PRS have Stickler Syndrome (AD) that includes other findings – early arthritis and ocular problems
- DD: Treacher Collin (mandibulo-facial dysostosis), Hemifacial microsomia, Goldenhar Syndrome
- Treatment: Address airway, Prone position, do U/E (look for Bicarb retention)

Pradder Willi Syndrome

- Major criteria: Neonatal hypotonia, Excessive weight gain, Feeding problems, Facial features, Hypogonadism, Developmental delay, Hyperphagia
- Minor criteria: Decreased foetal activity, Behaviour problems, Sleep disturbances / sleep apnoea, Short stature, Hypopigmentation, Small hands & feet, Narrow hands & straight ulnar border, Eye abnormalities, Thick viscous saliva, Articular defects and Skin picking
- Diagnosis: Chromosomal analysis for methylation patterns in PWS, PCR or Southern Blot hybridization and FISH analysis – parental

Rubinstein-Taybi Syndrome *(Forfar)*

- Broad thumbs, great toes
- Severe mental retardation
- Characteristic facies: Antimongoloid slants, Mid face Hypoplasia, High arched palate
- Narrow beaked nose

Russell Silver Syndrome

- Growth delays, increased risk of learning disabilities
- Before birth is IUGR and after birth will be growth deficiency
- Clinodactyly, Hemihypertrophy – unequal asymmetrical growth

Smith-Lemli-Opitz Syndrome *(Nelson p2401)*

- Prenatal and post-natal growth retardation
- Ptosis
- Anteverted nares
- Broad alveolar ridges
- Syndactyly of 2^{nd} and 3^{rd} toes
- Microcephaly
- Severe mental retardation
- Types: Classical **type 1** (associated with pyloric stenosis) & **type 2** (associated with Hirschsprung disease, Cleft palate, Skeletal abnormalities

Treacher Collin Syndrome

- Malformation of external ears
- Hearing loss
- Breathing difficulties
- Abnormal down ward slant of palpebral fissures
- Craniofacial abnormalities
- Hypoplasia of certain bones of head
- Zygomatic complex and the jaw & cheek bones

Zelweger Syndrome – Cerebro-hepato-renal syndrome *(B Nelson p 263)*

- High forehead, Flat orbital ridges, Widely opened fontanels
- Hepatomegaly, Hypotonia, FTT, Seizures & nystagmus