Basic Concepts in Dysmorphology

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Outline

- Definition of dysmorphology
- Definition of terms routinely used in the description of birth defects
- Impact of malformations
- The difference between major & minor anomalies
- Approach to a dysmorphic individual:
  - Suspicion & analysis
  - Systematic physical examination
  - Confirmation of diagnosis
  - Intervention
- Summary
Definition of dysmorphismology

- The term “dysmorphismology” was first coined by Dr. David Smith, USA in 1960s.
- It implies study of human congenital defects and abnormalities of body structure that originate before birth.
- The term “dysmorphic” is used to describe individuals whose physical features are not usually found in other individuals with the same age or ethnic background.
- “Dys” (Greek)=disordered or abnormal and “Morph”=shape
Definition of terms routinely used in the description of birth defects

- **A malformed / anomaly**: is a primary defect where there is a basic alteration of structure, usually occurring before 10 weeks of gestation.
- Examples: cleft palate, anencephaly, agenesis of limb or part of a limb.

Cleft lip & palate

Absence of digits (ectrodactyly)
• **Malformation Sequence:** A pattern of multiple defects resulting from a single primary malformation.
• For example: talipes and hydrocephalus can result from a lumbar neural tube defect.

Lumbar myelomeningocele
• **Malformation Syndrome:** A pattern of features, often with an underlying cause, that arises from several different errors in morphogenesis.

• “Syndrome” from the Greek “running together”.

• **Causes of syndromes:**
  - Single gene disorders (e.g. Apert syndrome)
  - Chromosomal disorders (e.g. Down syndrome)
  - Microdeletion syndromes (e.g. Prader-Willi syndrome)
  - Polygenic disorders (e.g. club foot)
  - Environmental causes (Teratogenesis) (e.g. Rubella, congenital viral infection, infant of diabetic mother)
Hands & feet of a patient with Apert syndrome

Down syndrome

Prader-Willi syndrome

Infant of diabetic mother with caudal regression

Club foot
- **Association:** An association is a group of anomalies that occur more frequently than would be expected by chance alone but that do not have a predictable pattern or unified etiology (e.g. VATER association).

Vertebral anomalies, absence of radius & anal atresia as a part of VATER association

Deformation: Distortion by a physical force of an otherwise normal structure. This could be due to uterine malformation, twins or oligohydramnios (e.g. contractures of limbs and talipes deformity.)

Multiple joint contractures (arthrogryposis)  
Talipes deformity
• **Disruption:** Destruction of a tissue that was previously normal. Examples of disruptive agents include amniotic bands, local tissue ischemia or hemorrhage.

Congenital ring constrictions with amniotic bands
**Dysplasia:** Abnormal cellular organization within tissue resulting in structural changes. For example within cartilage or bone in skeletal dysplasias (e.g. achondroplasia).

Radiological findings in achondroplasia: Loss of caudal widening (1), short long bones of lower limbs (2)

Characteristic features of achondroplasia
Impact of malformations

• About 3% of all children born will have a significant congenital malformation.
• These congenital malformations are responsible for a large proportion of neonatal and infant deaths.
• They also account for about 30% of all admissions to pediatric hospitals.
• It is important to recognize both major and minor malformations as they may lead to the early detection and intervention of a genetic disorder.
The difference between major and minor anomalies

- **Major anomalies** are severe, impair normal body function and require surgery for management (e.g. cleft palate, congenital heart disease). They may be isolated or multiple affecting different body systems.

- **Minor anomalies** are primarily of cosmetic significance (e.g. small ear, fifth finger clinodactyly). They occur with variable frequencies in the normal population.
## Significance of minor anomalies

| Occurrence of **single** minor anomaly | **15%** of all newborns  
3% have an associated **major** anomaly |
|---------------------------------------|--------------------------------------|
| Occurrence of **two** minor anomalies  | **Less common**  
11% have an associated **major** anomaly |
| Presence of **3 or more** minor anomalies | **Unusual 1%**  
90% have an associated **major** anomaly |
| **42% of idiopathic MR** have **3 or more** anomalies | **80%** of which are **minor** anomalies |
| External minor anomalies in the **head** and neck region and the **hand** | **Constitutes 71% of minor anomalies** |
Approach to a dysmorphic individual

I- Suspicion & Analysis

A genetic etiology should be suspected if the child has:

- Congenital anomalies (e.g., major anomaly or > 2 minor anomalies)
- Growth deficit (e.g., short stature or failure to thrive)
- Developmental delay, mental deficit or developmental regression
- Failure to develop secondary sexual characteristics
- Ambiguous genitalia
- Funny looking kid (FLK)
1. History:

   - Pedigree:

     Consanguinity increases the risk for an autosomal recessive (AR) disorder

     [Family pedigree diagram]

     Family pedigree suggestive of an AR disorder
Male patient with similarly affected male siblings or maternal male relatives suggests X-linked disorder.

Family pedigree suggestive of an X-linked disorder
Vertical transmission suggests an autosomal dominant (AD) disorder, specially male to male transmission.

Family pedigree suggestive of an AD disorder
History of miscarriages, stillbirths or early neonatal deaths suggests the possibility of a parental balanced chromosome rearrangement.

Family pedigree with multiple stillbirths and abortions
• **Pregnancy & family history:**
  - History of uterine malformations or oligohydramnios may suggest a possible aberrant force causing malformation.
  - Abnormal fetal position or weak fetal movements suggest abnormal fetal tone.
  - Placental morphology may give clue to the diagnosis (e.g. large placenta in Beckwith-Wiedemann syndrome).
  - Birth measurements, as symmetrical intrauterine growth retardation (IUGR) suggests early onset whereas, asymmetrical IUGR suggests late onset.
Environmental hazards for the fetus:
- Infectious agents (e.g. viruses, bacteria, parasites…)
- Physical agents (e.g. radiation, heat….)
- Drugs & chemicals
- Maternal factors (e.g. diabetes mellitus, hypertension, phenylketonuria…….)

History of growth & Development

Previous investigations
2. Physical examination:

**General principles:**

- Determine if the feature is a major anomaly, minor anomaly or a normal variant.
- Compare with other family members.
- Anthropometric measurements should be used whenever possible to quantitatively identify abnormalities.
- The growth of different parts of the body and face can be measured and the degree of abnormality is established by calculating the difference between the finding and the appropriate terminal value of the normal range using age, sex and ethnic appropriate standards.
Findings that suggest a possible underlying etiology:

**General**

- Short stature (height below -3SD) or tall stature (height above +3SD) (SD=standard deviation)

A short father & son with spondylo-epi-metaphyseal dysplasia

Short female with Turner syndrome
- Failure to thrive (height & weight below -3SD) or obesity (weight above +3SD)
Specific organ anomalies
Unusual head shape

Dolichcephaly

Brachycephaly

Trigonocephaly

Plagiocephaly

Oxycephaly

Cloverleaf skull

Brachycephaly (flat occiput)
**Head circumference**

e.g. small head “microcephaly” (head circumference below -3SD) or large head “macrocephaly”) (HC above +3SD)
**Body proportions**
e.g. short spine, short limbs or long limbs…

Disproportionate shortening in patients with mucopolysaccharidosis (1) & an autosomal recessive type of spondylo-epi-metaphyseal dysplasia (2)
Facial features

- **Eyebrows**
  e.g. Synophrys (fused eyebrows)

- **Innercanthal distance**
  e.g. Hypotelorism (decreased inner canthal distance or hypertelorism (increased inner canthal distance)
• **Palpebral fissures (slanting)**

Upslanting of palpebral fissures (e.g. Down syndrome)

or downslanting of palpebral fissures (e.g. Noonan syndrome & Rubinstein-Taybi syndrome)
- **Palpebral fissures (length)**

  Short palpebral fissures (the length of the palpebral fissure is usually equal to the distance between the two eyes i.e. innercanthal distance)

  ![Images of different eye conditions]

  - Blephrophimosis
  - Unilateral microphthalmia (small eye)
  - Unilateral anophthalmia (absent eye globe)
  - Bilateral anophthalmia
- **Eyes**
  
e.g. corneal opacities, heterochromia or other eye abnormalities

- Corneal opacity
- Heterochromia
- Albinism
- Squint
- Congenital glaucoma
Cataract

Epibulbar dermoid

Bilateral ptosis of eyelids
• Nose

Short or long nose (the nose is usually 2/3 – 3/4 the length of the distance between the nasal bridge and the upper lip)
• **Ears**

Abnormal ear position (low-set, posteriorly rotated…). When drawing an imaginary line between the outer canthus and the occiput, usually 1/3 of the ear is above this line)

[Image: Low-set, posteriorly rotated ear]

[Image: Low-set ears]
Abnormal shape or size of the ears

- Cupped simple ears
- Preauricular pit
- Cauliflower ears
- Microtia (small or dysplastic ears)
- Preauricular skin tags
• **Mouth & lips**

Abnormal lips (thin/full, tented, down turned, cleft), big or small mouth (macrostomia or microstomia)

- Thin tented lips
- Thick patulous lips
- Cleft lip
- Lip pits
- Macrostomia
- Microstomia
- Philtrum
  e.g. short, long or flat

  Short philtrum

  Long flat philtrum
• Oral cavity, tongue, palate & mandible

Tongue (e.g. macroglossia, bifid tip…)
Palate (high arched or cleft)
Uvula (bifid or absent)
Prognathism, micrognathia (small mandible), pointed chin

Macroglossia (large tongue) with bifid tip
Micrognathia
Bifid uvula
Pointed chin
Hands & feet

Brachydactyly (short fingers or toes)

Arachnodactyly (long fingers or toes)
Clinodactyly (incurved fingers, usually fifth finger)

Syndactyly (fusion of digits)
Reduction (absence) defect

Hemimelia (absent forearm & hand)

Ectrodactyly (absent toes)

Apodia (absent foot)

Axial hand reduction (split hands)
Polydactyly (preaxial, postaxial extra digits)

Postaxial polydactyly (pedunculated post minimus)

Complete postaxial polydactyly

Camptodactyly (contracture of fingers)
Polysyndactyly (preaxial polydactyly with syndactyly)
Nails & dermatoglyphics

Dysplastic nails with polydactyly

Simian crease

Abnormal flexion creases
Other limb anomalies

- Rocker bottom feet with sandal gap between 1\textsuperscript{st} & 2\textsuperscript{nd} toes
- Macrodactyly (large digits)
- Clasped thumb (adducted & flexed)
Skin

e.g. pigmentation, scales, pterygium, appendages....

Areas of hyper & hypopigmentation of skin

Facial hemangioma

Café-au-lait spots

Hypopigmented area on the forehead

Generalized hypopigmentation
Skin nevus
Dry scaly skin
Skin nevus
Cutis marmorata
Hemihypertrophy with multiple skin nevi
Knee pterygium
Skin appendages
Hair
Abnormal amount of hair (alopecia, hirsutism, hypertrichosis)

Generalized hirsutism

Hypertrichosis (long eye lashes) & synophros

Alopecia
Abnormal hair line (low hair line or receding hair line)
Abnormal hair color (e.g. white forelock, albinism)

Receding anterior hair line with hair hypopigmentation

Silver colored hair

Hypopigmentation of hair as a part of vitiligo

Anterior hair whorl
Neck
e.g. short, webbed…

Webbed neck

Chest
Abnormal chest shape (e.g. pectus carinatum, pectus excavatum, short sternum)

Pectus carinatum
Pectus excavatum
Nipples

e.g. widely spaced, supernumerary, inverted....

Widely spaced nipples

Supernumerary nipple
**Spine**

e.g. anencephaly, encephalocele, myelomeningocele or stigmata of spina bifida

- Anencephaly
- Myelomeningocele
- Encephalocele
Abnormal joint shape or mobility

Hyper extensibility of wrist joint

Hyper extensibility of knee joint (genu recurvatum)
Joint & bone deformities

- Bow knees
- Knock knees
- Knee joint dislocation
- Multiple bony fractures & deformities
**Abdomen**

Abdominal wall defects (omphalocele, gastroschisis)
Hepatosplenomegaly
Nephromegaly

- Umbilical hernia
- Gastrochisis
- Hepatosplenomegaly
Genitalia

e.g. ambiguous genitalia

Micropenis

Clitromegaly
46,XX DSD
II- Confirmation of diagnosis:

Lab. tests:

- Indications for chromosome analysis:
  - Multiple congenital anomalies
  - Ambiguous genitalia
  - Developmental delay with major and/or minor anomalies
  - History of more than 2 miscarriages

- Indications for metabolic screening:
  - Metabolic disorders known to cause dysmorphism are lysosomal disorders, peroxisomal disorders and disorders of cholesterol synthesis

- Radiological examination for bony changes and neuroimaging of brain structures.

Clinical course

Similarly affected family members
III- Intervention:

Treatment:
- Symptoms
- Underlying cause

Counselling:
- Diagnosis, natural history, prognosis, management
- Recurrence risk
- Reproductive

Follow-up:
- Identification and counselling of at risk family members
- Surveillance for complications
- Correction of diagnosis
Summary

- A congenital anomaly or birth defect is an abnormality of structure or function that is present at birth.
- Birth defects may be mild or serious.
- The principles in dysmorphology include the determination of the underlying pathogenic mechanism and if it is a single system or multi-system defect.
- Accurate identification of a syndrome is a necessary prerequisite to providing a prognosis and plan of management for the affected infant as well as genetic counseling for the parents.
Summary (Cont.)

- The first step towards an accurate diagnosis of a syndrome is by extensive phenotypic analysis.
- The severity and number of anomalies in a given syndrome vary from patient to patient.
- The number of malformation syndromes described is increasing everyday.
- It is better to refer to a clinical geneticist who is more familiar with these conditions, has access to specific laboratory studies, dysmorphology databases and is able to interpret the results and provide genetic counselling.
Useful Resources

- Jones KL. Smith’s Recognizable Patterns of Human Malformations: Expert Consult Online and Print. 6th ed. Saunders, 2005
Useful Resources

- Literature search e.g. PubMed
- Database search:
  - LMD: London Medical Databases by Winter R & Baraitser M. info@lmdatabases.com

NB: Most of the figures included in this presentation are from personal experience, few figures are retrieved from the internet.