Approach to a Child with Dysmorphism/ Congenital Malformation

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Definition

Dysmorphology is a discipline of clinical genetics which deals with the study of abnormal patterns of human growth and with the recognition and study of congenital human structural anomalies and patterns of birth defects.

Congenital malformations/ birth defects can be sub-classified as major or minor anomalies.

- **Major anomalies** are those that interfere with the normal functioning of an individual and pose a significant health problem or risk to life. E.g. congenital heart defects, neural tube defects, omphalocele, cleft palate etc.

- **Minor anomalies** do not interfere with the normal functioning of an individual and usually are only of cosmetic significance. E.g. simian crease, accessory nipple, cleinodactyly, pre-auricular skin tag etc.

Major anomalies are present in 2 -3 % and minor anomalies are present in around 15% of live births. Minor anomalies are usually associated with an increased risk of associated major anomalies and therefore presence of minor anomalies should prompt a thorough search for associated major anomalies.

Classification of congenital anomalies

Congenital anomalies are classified, on the basis of the developmental stage in which the insult occurred, the process that caused the change and the end result, into:

- **Malformation:** Primary intrinsic developmental defect usually caused by genetic/ environmental/ multi-factorial causes (recurrence risk varies accordingly) which occur during the period of organogenesis which is up to 8 weeks post fertilization for most organs. E.g. neural tube defect, ventricular septal defect, polydactyly etc.

- **Deformation:** Distortion of a normally developed structure caused by mechanical forces usually in the latter half of gestation and most often involving musculo-skeletal tissues. E.g. club foot, torticollis, plagiocephaly etc.

- **Disruption:** Breakdown of an intrinsically normally developing/ developed tissue due to some disruptive event such as a mechanical, vascular or infectious insult. E.g. amniotic band sequence.

- **Dysplasia:** Abnormal cellular organization within a tissue, almost always of genetic origin. E.g. skeletal dysplasias.

A syndrome is a recognized composite pattern of 2 or more anomalies with a common specific aetiology. E.g. Turner syndrome, fetal phenytoin syndrome etc.

An association is a non-random occurrence of 2 or more anomalies that occur together more frequently than expected by chance alone, but without a known specific aetiology. E.g. VACTERL association.

A sequence is a pattern of anomalies resulting from a single primary anomaly or factor E.g. Potter sequence (Primary anomaly - bilateral renal aplasia/ dysplasia→decreased fetal urine production→ severe oligohydramnios → compressive effects → flattened facies with flattened nose, deformed ears, pulmonary hypoplasia & positional limb defects).

Approach to a dysmorphic child

1. Suspicion
2. Clinical evaluation
   - history
   - physical examination
3. Investigations
4. Analysis and diagnosis
5. Confirmation
6. Intervention:
   - treatment
   - counseling
   - prenatal diagnosis
7. Surveillance & follow up

Suspicion:

Genetic etiology suspected in any child with:

- Congenital anomalies: at least 1 major/ > 2 minor anomalies.
- Growth deficit (short stature/ failure to thrive)
- Developmental delay, mental deficit or developmental regression
- Failure to develop secondary sexual characteristics
- Abnormal genitalia
- Appears 'different'/ 'unusual'

History:

- **Prenatal history:**
  - Teratogenic exposures: infections/ medications/ drugs of abuse/ maternal illness/ radiation
  - Prenatal complications& antenatal USG findings

- **Perinatal history:**
  - Presentation/ mode/ complications of delivery
  - Gestational age and condition (Apgar score) at birth
  - Birth weight; birth length & HC; size & proportions

- **Neonatal course:**
  - Feeding, activity and complications

- **Post neonatal:**
  - Physical growth & developmental milestones
  - Neurological symptoms esp. seizures / visual or hearing deficits/ behavioural phenotype
  - Other systemic symptoms

- **Family history:**
  - 3 generation family history / pedigree
  - History of recurrent pregnancy losses/ infertility
  - Specific information/ medical records of previously affected babies/relatives
  - Consanguinity in parents
  - Ethnic background

Physical examination

General principles:

- Thorough head to toe examination
- Take measurements & compare with standard tables/ graphs of age and gender norms.
- Examine both parents and other available family members for similar/ related features.
- Take clinical photographs (with consent of the patient or parents/ guardians): for records/ syndrome search/ referral & study of evolution of phenotype.

- Take care not to make the patient or parents feel conscious or offended during the examination.

- Preferably do not discuss or make any comments about the dysmorphic features in front of the patient and family.

Anthropometric measurements:

- Height/ length; Weight; Head circumference

Assessment of proportionality & symmetry:

- Upper segment/ lower segment ratio; Arm span; Individual limb segment measurements (in specific cases)

Head to toe assessment: (for exact description of each feature refer to Am J Med Genet A 2009 Jan; 149A (1) & Aase JM Diagnostic Dysmorphology).

- Carefully examine each body part from head to feet & look for anomalies

- Cranium – size/ fontanelles/ sutures/ shape & symmetry

- Scalp hair - colour & texture; distribution/ hair whorl patterns; position of anterior & posterior hairline, sweep of the hair

- Face

    o overall impression of facial appearance: **gestalt** e.g. Down syndrome facies; coarse facies; myopathic facies

    o overall shape/ symmetry/ size of face: triangular/ broad/ round

    o divide the face into sections: forehead, midface & oral region

    o view face from front & from side

    o lateral profile better for: depth or height of structures such as nasal bridge, position of mandible relative to maxilla & midface development

- Facial measurements:

    o interpupillary distance, inner canthal distance, outer canthal distance, interalar distance, philtral length, upper lip thickness, lower lip thickness, intercommisural distance

    o Compare to age/ sex norms; < or > 2SD => abnormal

- Forehead - Size: small/ broad/ tall; Shape: sloping/ frontal bossing/ bitemporal narrowing/ metopic prominence; Supraorbital ridges: prominent/ underdeveloped

- Maxilla/ midface - Cheek bone: prominent/ underdeveloped/ fullness; Malar region: prominence/ flattening; Midface: prominence/ retrusion; Nasolabial folds: prominent/ underdeveloped

- Mandible - size & shape: micrognathia/ retrognathia/ prominence

- Eyes- eyebrows; palpebral fissure length (short/long); palpebral fissure slant (up/down); epicanthic folds ; eye spacing (use a rough guide of 1:1:1 for ratio of left palpebral fissure length: inner canthal distance: right palpebral fissure length); palpebral fissure shape; iris colour; pupil shape; cornea/ sclera/ lens; globe position (assessed from lateral view: protuberant vs deep set globes)

- Nose - Divide into 3 sections from lateral view from superior to inferior: Nasal root; Nasal bridge : depressed/prominent/broad; Nasal tip: broad/ flattened; Columella (the vertical ridge separating the nostrils): wide/ overhanging; Nostrils : patency & position (anteverted); Alae nasi: hypoplastic

- Mouth & perioral region - mouth size and shape; lip shape, thickness; gum thickness; philtrum definition and length; jaw position (prognathia/micrognathia); palate shape; oral cavity - teeth/ frenulum/ tongue size and morphology

- Ears - Ear position; ear rotation (normally 15 degrees posterior to the vertical plane of the head): anteriorly/ posteriorly rotated; Ear shape and structure; Accessory structures: pits/ skin tags

- Skeleton-

    o Neck: length/ shape (webbed)

    o Shape of thoracic cage

    o Sternum: length & shape (pectus carinatum/excavatum)

    o Spine: length/ straight/curved

    o Limbs: length/shape/ symmetry

- Joints – contractures; range of joint movement: laxity/ restriction; soft tissue webbing across joints (pterygium)

- Skin –

    o Texture: smooth/ coarse/ dry/ ichthyotic

    o Pigmentation: hypo/ hyperpigmentation; patchy / generalized

    o Naevi/ lentigines

    o Redundancy/ laxity

    o Patchy pigmentation may indicate mosaicism

- Hands and Feet - overall shape and size of hand and foot; digit number; digit shape (e.g. cleinodactyly) and length; webbing between digits; palmar, plantar and digit creases; nail morphology

- Genitalia and Anus

    o phallus size & morphology

    o development, rugosity & pigmentation of scrotum

- o size & position of testes

- o development of labia

- o position of anus relative to genitalia, patency of anus

Systemic Examination: cardiovascular/ per abdomen/ neurological/ respiratory

Physical features not found as normal/ familial traits and present in specific conditions are of more diagnostic help: 'good handles' for diagnosis e.g. epibulbar dermoid for Goldenhar syndrome

Radiographs

- Xray wrist + hand (AP view) in short stature: for bone age assessment

- Genetic skeletal survey for suspected skeletal dysplasias/ disproportionate short stature:

    - AP & lateral views of skull

    - AP & lateral views of spine (cervical to sacrum)

    - AP of pelvis with bilateral hip joints

    - AP of 1 hand & 1 foot

    - AP of 1 upper limb (shoulder to elbow; elbow to wrist)

    - AP of 1 leg (knee to ankle)

Imaging

- Neuroimaging:

    - MRI brain: in presence of neurological deficits/ seizures/ microcephaly or microcephaly/ clinical suspision of a syndrome known to be associated with brain malformations (e.g. Molar tooth sign in Joubert syndrome)

    - CT Scan: suspected TORCH infections/ cranial contour abnormalities/ craniosynostosis (3D CT)

- USG abdomen/ 2D Echo: to look for visceral malformations

Analysis

- Put all findings together and make a diagnosis into which all features can fit

- If unable to identify syndrome based on experience, use resources – Dysmorphology database (London Dysmorphology DataBase/ POSSUM); online resources (OMIM – Online Mendelian Inheritance in Man) & Gamuts of Taybi and Lachman's radiology of syndromes, metabolic disorders and skeletal dysplasias (http://www.taybiandlachman.com/), Dysmorphology textbooks etc.

Genetic Testing

Karyotyping: in cases with

- multiple malformations
- prenatal onset growth retardation
- disorder of sexual development
- developmental delay
- history of multiple miscarriages in the family

Fluorescence in situ hybridization (FISH)/ Multiplex ligation - dependent probe amplification (MLPA): phenotype suggestive of a specific microdeletion syndrome e.g. Di George syndrome (22q)/ Angelman syndrome (15q)/ Williams syndrome (7q)

Metabolic testing:

If specific metabolic disorder is identified; metabolic disorders with dysmorphism include:

- Mucopolysaccharidoses, oligosaccharidoses, mucolipidosis, GM1 gangliosidosis
- Peroxisomal disorders
- Disorders of cholesterol metabolism (e.g. Smith Lemli Opitz syndrome)

Single gene mutation analysis: PCR based test or whole gene sequencing when a specific monogenic disorder is suspected

Cytogenetic microarray study:

- Can be done in any case with multiple malformations with or without associated intellectual disability and without any other identified genetic/ nongenetic cause
- Scans the entire genome for copy number variations (microdeletions/ microduplications)

Intervention

- Appropriate medical/ surgical management wherever feasible: eg. surgical correction of cardiac defect, correction of hearing deficit etc.
- Genetic counseling
- Prenatal diagnosis wherever feasible

Genetic Counseling

- Deformations/ disruptions have low risk of recurrence
- Denovo chromosomal abnormalities/ microdeletions have risk of recurrence of <1%

- Familial chromosomal rearrangements have a variable recurrence risk – depending on the type and the chromosomes involved

- In single gene disorders, risk of recurrence will vary according to mode of inheritance: AD/ AR/ XL

Prenatal Diagnosis

- Targeted mutation analysis/ chromosomal analysis/ metabolic testing in fetal tissue depending upon diagnosis of proband: Chorionic villus sample/ amniotic fluid/ pre-implantation genetic diagnosis

- Fetal anomaly scan to look for the same/ associated malformations

- 3D/ 4D USG can pick up the facial profile/ external dysmorphisms better

- Fetal echocardiogram for detecting fetal cardiac anomalies

- Limitations of scan based prenatal diagnosis: cannot detect certain malformations like imperforate anus; cannot determine intellectual status; cannot pick up some features eg microcephaly/ lissencephaly until late gestation

Follow up

- To assess growth & development

- To study course of the disease

- To monitor for known/ anticipated associated complications

- To offer newly available diagnostic tests

- To offer newly available therapeutic options

- Sometimes phenotype evolves with age & reassessment at a later age in an undiagnosed case might make diagnosis clear

- To discuss reproductive risks.

Resources for reference

- Books:

  - Aase JM. Diagnostic Dysmorphology.

  - Taybi and Lachman's Radiology of Syndromes, Metabolic Disorders and Skeletal Dysplasias.

  - Gorlin RJ, Cohen MM, Levin LS. Syndromes of the head and neck.

  - Hall JG, Froster-Iskenius I, Allanson J. Handbook of physical measurements.

  - Jones KL. Smith's recognizable patterns of human malformations.

  - Sadler TW. Langman's medical embryology.

- o Stevenson RE, Hall JG. Human malformations and related anomalies.
- Databases:
  - o OMIM (Online Mendelian Inheritance in Man)
  - o POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)
  - o Winter RM, Baraitser M. London Dysmorphology Database