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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, clinodactyly, 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 cause. 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 (vertebral defects, anal atresia or stenosis, cardiac defects, tracheo-esophageal fistula, radial defects and renal anomalies, limb defects) 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 case with dysmorphism

The following step-wise clinical approach should be followed in the assessment and management of an individual with dysmorphism or congenital malformation(s):

1. Suspicion of a genetic etiology
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 of a genetic etiology

A genetic aetiology should be suspected in any individual with the following:

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

History

A detailed history covering the following aspects should be obtained:

- Prenatal history:
  - Teratogenic exposures especially in the first trimester of pregnancy: infections/ medications/ drugs of abuse/ maternal illness/ radiation exposure
  - Prenatal complications and antenatal ultrasonographic findings
- Perinatal history:
  - Presentation/ mode/ complications of delivery
  - Gestational age and condition (Apgar score) at birth
  - Birth weight, birth length and head circumference; body proportions
- Neonatal course:
  - Feeding and activity
  - Any adverse events/ complications
- Post neonatal:
  - Physical growth
  - Developmental milestones
  - Neurological symptoms especially seizures / visual or hearing deficits/ behavioural phenotype
  - Other systemic symptoms
- Family history:
  - At least three generation family history / pedigree
  - History of recurrent pregnancy losses/ infertility
  - Specific information/ medical records of other affected family members
  - Consanguinity in parents
  - Ethnic background

Physical examination

A thorough clinical examination must be done taking the following aspects into consideration:

- General principles:
  - Thorough head to toe examination to be done.
  - Measurements to be taken and compared with standard tables/ graphs of age and gender norms.
  - Both parents and other available family members to be examined for similar or related features.

  - Clinical photographs to be taken with informed consent of individual/ parent/ guardian: for records, syndrome search, referral and study of evolution of the phenotype.

- 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 textbook).
  - Each body part to be examined carefully from head to feet to look for anomalies
  - Cranium – size; fontanelles; sutures; shape and symmetry
  - Scalp hair - colour and texture; distribution; hair whorl patterns; position of anterior and posterior hairline
  - Face
    * overall impression of facial appearance: *gestalt* e.g. Down syndrome facies, coarse facies, myopathic facies
    * overall shape, symmetry and size of face: triangular/ broad/ round
    * face to be divided into sections: forehead, midface and oral region
    * face to be viewed from front and from side
    * lateral profile better for: depth or height of structures such as nasal bridge, position of mandible relative to maxilla and midface development
  - Facial measurements:
    * Interpupillary distance, inner canthal distance, outer canthal distance, interalar distance, philtral length, upper lip thickness, lower lip thickness, intercommisural distance
    * Measurements to be compared to age and sex norms ($<$ or $>$ 2SD $\Rightarrow$ 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 – nasal root; nasal bridge : depressed/prominent/broad; nasal tip: broad/ flattened; columella (the vertical ridge separating the nostrils): wide/ overhanging; nostrils : patency and position (anteverted); alae nasi
  - Mouth and perioral region - mouth size and shape; upper and lower lip shape and 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-
    * Neck: length/ shape (webbed)
    * Shape of thoracic cage
    * Sternum: length & shape (pectus carinatum/excavatum)
    * Spine: length/ straight/curved
    * Limbs: length/shape/ symmetry

- Joints – contractures; range of joint movement: laxity/ restriction; soft tissue webbing across joints (pterygium)
- Skin –
  * Texture: smooth/ coarse/ dry/ ichthyotic
  * Pigmentation: hypo/ hyperpigmentation; patchy / generalized
  * Naevi/ lentigines
  * Redundancy/ laxity
  * Patchy pigmentation may indicate mosaicism
- Hands and Feet
  * Overall shape and size of hand and foot
  * Digit number
  * Digit shape (e.g. clinodactyly) and length
  * Webbing between digits
  * Palmar, plantar and digit creases
  * Nail morphology
- Genitalia and Anus
  * Phallus size and morphology
  * Development, rugosity & pigmentation of scrotum
  * Size and position of testes
  * Development of labia
  * Position of anus relative to genitalia and patency of anus

- Systemic Examination: cardiovascular/ per abdomen/ neurological/ respiratory
- Physical features not found as normal or familial traits and which are present in only a few conditions or are pathognomonic of specific disorders are of more diagnostic help. These are said to be 'good handles' for diagnosis e.g. white forelock of hair which is a good diagnostic clue for Waardenburg syndrome.

Radiographs

The following radiographic assessment helps in the diagnostic evaluation:

- X ray wrist + hand (anteroposterior (AP) view) in cases with 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 view of pelvis with bilateral hip joints
  - AP view of one hand and one foot
  - AP view of one upper limb (shoulder to elbow; elbow to wrist)
  - AP view of one leg (knee to ankle)

Imaging studies

The following imaging modalities may be used in the evaluation:

- Neuroimaging:
  - MRI brain: in presence of neurological deficits/ seizures/ microcephaly or macrocephaly
  - CT Scan brain: for suspected TORCH infections/ cranial contour abnormalities/ craniosynostosis (3D CT)
- USG abdomen/ 2D Echo: to look for visceral malformations

Analysis

- All clinical and laboratory findings must be analysed together in order to get a diagnosis; all features must fit into the diagnosis as far as possible
- If the condition cannot be diagnosed based on previous experience or existing knowledge, one should take the help of resources such as dysmorphology databases (e.g. LDDB - London Dysmorphology DataBase and POSSUM – Pictures of Standard Syndromes and Undiagnosed Malformations), online resources (OMIM – Online Mendelian Inheritance in Man) and dysmorphology textbooks.

Genetic Testing

The following genetic tests can help in confirming the aetiology in affected cases:

- Karyotyping: to be done in cases with:
  - congenital 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): when the phenotype is suggestive of a specific microdeletion syndrome e.g. Di George syndrome (22q microdeletion)/ Angelman syndrome (15q microdeletion)/ Williams syndrome (7q microdeletion)
- Metabolic testing: Relevant biochemical investigations should be done if a metabolic etiology is suspected. 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: DNA-based molecular genetic tests to be done when a specific monogenic disorder is suspected.
- Cytogenetic microarray (CMA) study:

  - Can be done in any case with multiple malformations with or without associated intellectual disability and without any other identified genetic/ non-genetic cause
  - CMA 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 (but can recur if the causative intrauterine environmental factor persists or recurs in the next pregnancy).
- Denovo chromosomal abnormalities and microdeletions have a risk of recurrence of $< 1\%$
- In single gene disorders, risk of recurrence will vary according to the mode of inheritance: autosomal dominant (50% in sibs and offspring if inherited and nil in sibs if de novo)/ autosomal recessive (25% in sibs)/ X-linked (50% in male sibs)

Prenatal Diagnosis

- Targeted mutation analysis/ chromosomal analysis/ metabolic testing in fetal tissue depending upon diagnosis of proband: Chorionic villus sample/ amniotic fluid/ preimplantation genetic diagnosis
- Fetal anomaly scan to look for the same/ associated malformations
- 3D/ 4D USG for better visualisation of the facial profile/ external dysmorphisms
- Fetal echocardiogram for detecting fetal cardiac anomalies
- Limitations of scan based prenatal diagnosis:

  - may not be able to detect certain malformations especially gut anomalies such as malrotation and lower GI obstruction
  - cannot determine intellectual status
  - cannot pick up some features e.g. 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 and 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. 1990. Springer.
  - Hennekam R, Allanson J, and Krantz I. Gorlin's Syndromes of the Head and Neck. Fifth edition; 2010. Oxford University Press.
  - Hall JG, Allanson JE, Gripp KW, Slavotinek AM. Handbook of Normal Physical Measurements. Second edition; 2007. Oxford University Press.
  - Jones KL. Smith's Recognizable Patterns of Human Malformation. Sixth edition; 2005. Elsevier.
  - Langman's Medical Embryology. Sadler TW. Twelfth edition; 2012. Lippincott Williams & Wilkins.
  - Stevenson RE, Hall JG. Human Malformations and Related Anomalies. Second edition; 2006. Oxford University Press.
- Databases:
  - OMIM (Online Mendelian Inheritance in Man) (`http://www.ncbi.nlm.nih.gov/omim`)
  - POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)
  - Winter RM, Baraitser M. London Dysmorphology Database

Announcement

Indo - US Symposium on Genomic Insights into Human Morphogenesis And First Annual Meeting of Society for Indian Academy of Medical Genetics

November 7th – 9th, 2014

Venue: Bhaskara Auditorium, B M Birla Science Centre, Hyderabad

The INDO-US symposium and conference will take you on an invigorating journey into the world of Developmental Dysmorphology, Syndrome Diagnosis, Prenatal Diagnosis, Genetic counseling, Molecular genetics and Next Generation sequencing.

Organized by:
Centre for DNA Fingerprinting and Diagnostics
Indo-US Science and Technology Forum
Society for Indian Academy of Medical Genetics

For details: http://www.indous2014.webs.com

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