Congenital Malformations

Definition / Supporting Information

A **malformation** (*eg, cleft lip, Tetralogy of Fallot)* is a congenital morphologic anomaly, of a single body part or organ, due to an alteration of the primary developmental programme. A malformation strictly differs from a **deformation**, which is the altered position or shape of an otherwise normal structure by an aberrant mechanical force, eg, talipes secondary to oligohydramnios.

A **disruption** is a non-progressive, congenital morphological anomaly, due to the breakdown of a body structure that had normal developmental potential, eg, amniotic bands.

A **dysplasia** is a morphological anomaly arising from a dynamic alteration of cellular form or function within a specific organ or tissue type, eg, skeletal dysplasias.

A **sequence** is one or more secondary morphological anomalies known or presumed to cascade from a single malformation, deformation, disruption of dysplasia, eg, Potter's Sequence.

All of the above can exist as isolated phenomena or be part of a broader pattern of anomalies, known or thought to be causally-related, in which case they tend to be known as a **syndrome**. For example, the Pierre-Robin Sequence can exist on its own or be part of a wider syndrome, such as Stickler's Syndrome. Syndromes should be distinguished from **associations**, which are patterns of anomalies, at least two of which are morphological that occur more often than would be expected by chance, but where a causal relation has not been identified. An association may therefore become a syndrome, with advances in knowledge, eg, CHARGE.

Essential History

Ask about:

- Natural or assisted conception
- Gestation and birth weight
- Induction of labour
- Vaginal, instrumental, or caesarean delivery
  - If caesarean, what was the indication?
  - Babies born from breech presentation are approximately four times more likely to have congenital malformations.
- The parents' ages at the time of the child's delivery
- Maternal health during pregnancy
  - Underlying medical problems

  - Medications
  - Smoking
  - Alcohol
  - Non-prescription drugs
- Scans in pregnancy
  - Abnormalities detected
- Additional tests / procedures in pregnancy
  - Free foetal DNA
  - Serum screening
  - Specific prenatal diagnosis
    - Chorion villous sampling
    - Amniocentesis
- Oligo / polyhydramnios
  - Reduced foetal movements
    - Quickening, which normally occurs between 16 and 20 weeks' gestation, is delayed in hypotonic foetuses, who also have less vigorous movements during foetal life.
- Previous operations or hospital admissions
- Medications
- Hearing and vision
- Developmental milestones, behaviour, and sleep pattern
- Family history
  - A three-generation pedigree should be drawn, searching for similar and dissimilar abnormalities in relatives.
  - A history of miscarriages, stillbirths, or neonatal deaths should be documented.
  - Consanguinity should be asked about in **all** cases.
  - Ethnicity should also be recorded, as some genetic conditions are more common in some ethnic groups than others.

'Red Flag' Symptoms and Signs

Ask about:

- Delayed development
- Feeding difficulties

Look for:

- Evidence of aspiration pneumonia
  - Tachypnoea and respiratory distress

- Evidence of cardiac disease
  - Murmur
  - Tachycardia
  - Hepatomegaly
  - Hypertension
- Abnormalities on detailed neurological examination

Differential Diagnosis / Conditions

- In most cases, no specific diagnosis is immediately evident.
- Clinical geneticists have attempted to resolve this difficulty by:
  - Developing clinical criteria, including scoring systems, for certain syndromes (eg, neurofibromatosis type I (NF1), Marfan's syndrome)
  - Computerised diagnostic programmes, cross-referencing dysmorphic features to potentially associated syndromes, such as the London Medical Database and POSSUM

Craniofacial features

- Head shape
  - Normocephaly
    - A normal head shape
  - Dolichocephaly or scaphocephaly
    - A long, thin head
  - Brachycephaly
    - A head that is narrow in the anteroposterior diameter and broad laterally
  - Plagiocephaly
    - A head that is asymmetric or lopsided
- Facial features
  - Examples of causes of genetic facial malformation
    - Chromosomal
      - Down's syndrome (trisomy 21; midface hypoplasia, upward obliquity of palpebral fissures, epicanthal folds, flat nasal bridge, anteversion of nares)
    - Autosomal dominant
      - Treacher Collins syndrome (dysplastic ears, maxillary hypoplasia)
    - Autosomal recessive
      - Hurler's syndrome (corneal clouding, coarse facies)
    - Teratogenic
      - Congenital rubella (cataracts)

        - Drug induced
            - Foetal alcohol syndrome (smooth philtrum, small eyes)
    - Facial asymmetry may be due to:
        - Deformation related to intrauterine or extrauterine positioning
        - Malformation of one side of the face
            - For example, hemifacial microsomia (Goldenhar's syndrome or facio-auriculo-vertebral syndrome)
- Forehead
    - Overt prominence
        - Achondroplasia
    - Deficiency
        - Sloping appearance, which occurs in children with primary microcephaly
- Midface
    - Encompasses the region from the eyebrows to the upper lip and laterally from the outer canthus of each eye to the outer commissure of the lips
    - Hypoplasia of the midface is a common component of many syndromes, including Down's syndrome and foetal alcohol syndrome.
    - The distance between the eyes
        - Inner and outer canthal distances
    - Pupils: interpupil distance
        - Eyes that are too close together (hypotelorism)
            - Holoprosencephaly
        - Eyes that are too far apart (hypertelorism)
            - Suggestive of such syndromes as Opitz's syndrome (ocular hypertelorism, tracheal and esophageal anomalies, and hypospadias)
    - Palpebral fissure length / obliquity
        - Short in foetal alcohol syndrome
        - Excessively long in Kabuki's syndrome (short stature, mental retardation, long palpebral fissures with eversion of lateral portion of lower lid)
        - The obliquity (slant) of the palpebral fissures may be upward, as in Down's syndrome, or downward, as in Treacher Collins syndrome.
    - Epicanthal folds, flaps of skin covering the inner canthus of the eye that are usually associated with flattening of the nasal bridge, may indicate Down's syndrome or foetal alcohol syndrome.
    - Features of the nose
        - Nasal bridge can be flattened, as in Down's syndrome, or prominent, as in velocardiofacial syndrome

- Malar region
  - Extends on either side from the upper portion of the ear to the midface
  - Ears should be checked for:
    - Shape
      - Noting abnormal folding or flattening of the helices
    - Position
      - Low set if the top of the ear is below a line drawn from the outer canthus to the occiput
        - May be low set because they are small or microtic or because of a malformation of the mandibular region
    - Orientation
      - Posterior rotation is present when ear appears turned toward the rear of the head.
- Mandibular region
  - The mandible extends from lower ear to lower ear and includes the lower lip and jaw.
  - If the mandible itself is small, it is described as micrognathic (Pierre Robin malformation sequence).
  - An unusually prominent mandible is described as prognathic.

Neck

- Webbing
  - A feature common in Turner's and Noonan's syndromes
- Shortening, occasionally seen in:
  - Some skeletal dysplasias
  - Conditions in which anomalies of the cervical spine occur (Klippel–Feil syndrome)

Trunk

- Chest should be examined for shape.
  - A shield-like chest is found in Noonan's and Turner's syndromes.
- Symmetry
  - Hypoplasia of the pectoralis major and minor muscles, leading to asymmetry (Poland malformation sequence)
- A pectus deformity of the chest, either pectus excavatum or pectus carinatum, is usually an isolated finding.
  - Also a cardinal feature of Marfan's syndrome
- Scoliosis is usually an isolated feature
  - Often seen in Marfan's syndrome and in several other disorders

- Vertebral anomalies
  - VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb anomalies)

Extremities

- The presence of single or multiple joint contractures suggests either:
  - Neuromuscular dysfunction, as in the case of some forms of muscular dystrophy, **or**
  - External deforming forces that limited motion of the joint in utero
- Radioulnar synostosis, an inability to pronate or supinate the elbow, occurs in:
  - Foetal alcohol syndrome
  - Some X chromosome aneuploidy syndromes, such as 48,XXXX and 48,XXXY syndromes
- Polydactyly: the presence of extra digits
  - In isolation as an autosomal-dominant trait in up to 1% of all newborns
  - As part of a malformation syndrome, such as trisomy 13
- Oligodactyly: a deficiency in the number of digits
  - Seen in Fanconi's syndrome (growth retardation, aplastic anaemia, development of leukemia or lymphoma, and associated heart, renal, and limb defects including radial aplasia and thumb malformation or aplasia)
  - Generally part of a more severe limb reduction defect or secondary to intrauterine amputation that may occur with amniotic band disruption sequence
- Syndactyly, a joining of two or more digits, is common to several syndromes.
- Dermatoglyphics
  - Transverse palmar crease, indicative of hypotonia during early foetal life (~50% of children with Down's syndrome and 10% of people in the general population)
    - A characteristic palmar crease pattern is seen in foetal alcohol syndrome.

Genitalia

- Ambiguous genitalia can be associated with endocrinological disorders, such as:
  - Congenital adrenal hyperplasia (female infants have masculinised external genitalia, but male genitals may be unaffected)
  - Chromosomal disorders, such as Turner's syndrome mosaicism
  - Part of a multiple malformation disorder, such as Smith–Lemli–Opitz syndrome
- Hypospadias (occurs in 1 in 300 male newborns) is a common congenital malformation that often occurs as an isolated defect.
  - If it is associated with other anomalies, the possibility of a syndrome is strong.

Growth

- Small size or growth restriction may be secondary to:
  - Chromosomal abnormality
  - Skeletal dysplasia such as achondroplasia
  - Exposure to toxic or teratogenic agents
- Larger-than-expected size suggests an overgrowth syndrome
  - If in the newborn period, suggests maternal diabetes
- Proportions
  - Short limbs imply presence of a short-limbed bone dysplasia, such as achondroplasia.
  - Trunk and head that are too small for the extremities may suggest a disorder affecting the vertebrae.

Investigations

Major dysmorphisms are usually noticed at birth or sometime between then and the 6–8 week check.

To be undertaken by specialist practitioners (eg, Paediatric / Genetic Team(s)):

- Baseline microarray (Comparative Genomic Hybridisation; CGH) analysis is indicated in most children in whom a syndromal diagnosis is being considered, the precise nature of which is not immediately obvious clinically, especially when there are any developmental problems.
- Facial photographs, appropriately consented of course, should be considered in the evaluation of dysmorphism.
- The presence of internal malformations should be considered, and investigated appropriately, in those individuals found to have multiple external malformations.
- Radiological imaging may play an important role in the evaluation of children with dysmorphic features, especially when there is short stature and / or disproportion.

Treatment Approach

Treatment is aimed at managing the specific conditions.

When to Refer

Refer urgently to specialist practitioners (eg, Emergency Department / Paediatric Team(s)) if:

- Any 'red flag' signs or symptoms

Escalate care of infants and children with congenital malformations to a Dysmorphologist (who is usually a Clinical Geneticist with a background in Paediatrics) in order to:

- Try to make a clinical diagnosis of a dysmorphic syndrome and / or co-ordinate further, specialist genetic testing
- Discuss the potential implications of a diagnosis to other family members, including prognosis, need for possible further health surveillance / screening, recurrence risks, potential for prenatal diagnosis in future pregnancies, carrier testing, etc.

'Safety-Netting' Advice

- Advise parents / carers to seek medical advice urgently if 'red flag' signs or symptoms develop.
- Many dysmorphisms can be managed in the community with the support of a multidisciplinary team.
- If the parents or carers have further concerns, they should raise these with the team who should be reviewing the child regularly.

Parent / Carer Information

Please note: whilst these resources have been developed to a high standard they may not be specific to children.

- Club foot – treatment (Web page), the NHS website
- Club foot – video (Web page), the NHS website
- Down's syndrome (Web page), the NHS website
- Screening for Down's, Edwards' and Patau's Syndrome's (Web page), the NHS website
- Genetics (Web page), the NHS website

Resources

National Clinical Guidance

Palate examination: Identification of cleft palate in the newborn - best practice guide (Web page), Royal College of Paediatrics and Child Health.

Suggested Resources

Please note: these resources include links to external websites. These resources may not have national accreditation and therefore PCO UK cannot guarantee the accuracy of the content.

CLAPA (Website), The Cleft Lip and Palate Association.

CRANE database (Website), The Royal College of Surgeons of England.

Contact a Family (Website), Contact a Family.

GeneTests (Website), GeneTests.

Genetic Alliance (Website), Genetic Alliance.

Cassidy SB, Allanson JE. Management of Genetic Syndromes. 3rd ed. Wiley-Blackwell; 2010.

National Organization for Rare Disorders (Web page), National Organization for Rare Disorders (NORD).

Online Mendelian Inheritance in Man (Web page), National Center for Biotechnology Information.

Jones K, Jones M, del Campo M. Smith's Recognizable Patterns of Human Malformation. 7th ed. Philadelphia, PA: Saunders; 2013.

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Gripp KW, Slavotinek AM, Hall JG, Allanson JE. Handbook of Physical Measurements. Oxford University Press; 2013.

Dysmorphology Database (Search tool), London Medical Databases.

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