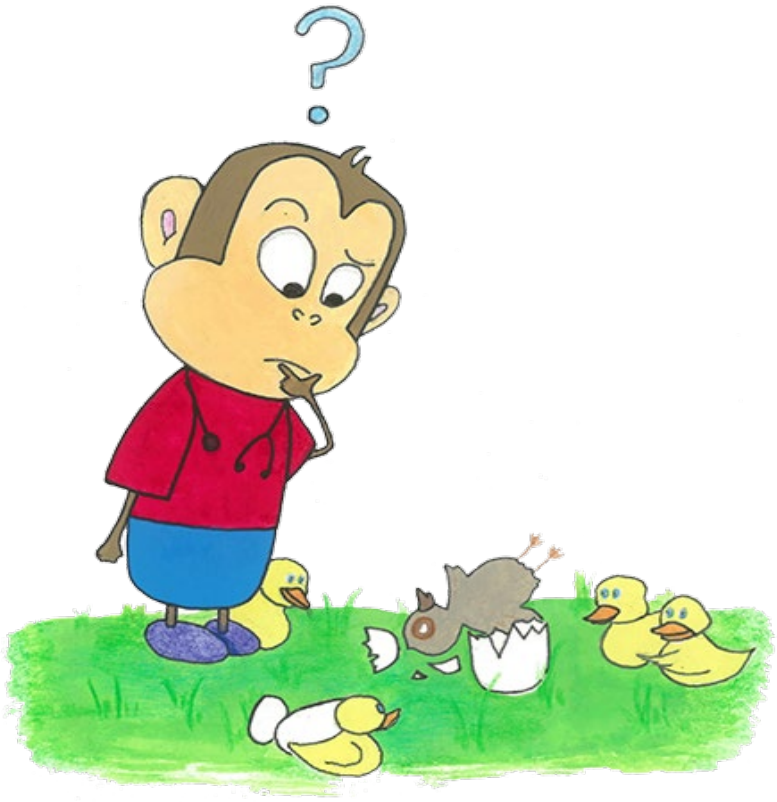
Chapter 1:

GENETICS AND CONGENITAL ANOMALIES

Student Authors: Kira Düsterwald

Specialist Advisors: Prof. Karen Fieggen and Gillian Düsterwald



This chapter covers the following topics:

- Approach to dysmorphism and structural congenital anomalies
- Down syndrome
- Other trisomies
- Sex chromosome disorders
- Foetal alcohol spectrum disorder
- Short, dysmorphic children
- Other genetic syndromes and disorders
- Genetic testing

APPROACH TO DYSMORPHISM AND STRUCTURAL CONGENITAL ANOMALIES

Occasionally, one will encounter a neonate or child who looks “different”. These children may have a single dysmorphic feature, or a group of features, suggestive of a syndrome, many of which are caused by genetic abnormalities and others by teratogens. Many of these children will also have one or more structural abnormalities and developmental delay, while others may have structural abnormalities without unusual characteristics.

It is important to know how to approach these children and what should be done at a primary care level, as well as when to refer to a secondary or tertiary unit. As in all clinical practice, a good history and thorough clinical examination should always be the first step. Particular attention should be paid to the family history and perinatal history. The child’s growth measurements should be charted and a full systematic examination conducted.

Unique Features in the Child with a Genetic Disorder

Multi-system involvement is common. A variant (genetic difference which is present at conception) will usually be present in every cell of the body. This is especially true if the variance is due to teratogenicity (teratogens can act on various systems). Specialist care and treatment may be needed and the child is often best managed by a multidisciplinary team. For example, the child may need to be referred to a medical geneticist or other specialist to assist in diagnosis and management.

Additionally, the patient and his/her family may need specialised health care and psychosocial support for the rest of their lives, especially with conditions where there is a risk of recurrence of the disease in the affected child, future sibling and extended family members.

Aetiology of Dysmorphic Syndromes and Congenital Anomalies

There are different causes for dysmorphic syndromes and congenital anomalies, not all of which are hereditary. However, all causes affect cellular function in some way.

- Genetic causes:
    - Chromosomal anomalies:

        - They may be abnormalities of number (monosomy, trisomy) or structure (translocation or deletion) and include gains or losses of long segments of DNA.
        - These anomalies may be inherited or, more frequently, “de novo” (occur for the first time in the affected child).
    - Single gene mutations:
        - They include changes in the nucleotide sequence of one particular gene (e.g. deletions, insertions or substitutions) and are inherited in different ways.
        - Autosomal dominant disorders only require one copy of the abnormal gene to cause the disorder (commonly de novo in a severe, early-onset condition).
        - Autosomal recessive disorders require both copies of a gene to be abnormal to cause the disorder.
        - Sex-linked disease occurs when the gene is on the X chromosome. If the disorder is recessive, one normal copy of the two X chromosomes is largely protective (i.e. in females) and males are affected (as they have only one X chromosome).
        - Mitochondrial genome disorders are only maternally passed on.
    - Multifactorial causes imply multiple, smaller genetic and environmental contributors.
- Teratogenic causes:
    - Teratogens are external factors which disturb in-utero development, usually in early pregnancy). They may include:
        - Maternal medication e.g. sodium valproate
        - Maternal recreational drug exposure (especially alcohol)
        - Maternal illness e.g. diabetes
        - Congenital infections e.g. rubella
- Unknown aetiology (at least 30% of cases)

When to Suspect an Underlying Genetic or Syndromic Disorder

The features listed below should prompt you to look closely for additional features and, if appropriate, to refer for further evaluation. The clinician's suspicion should increase if any of the below occur together:

- Major structural abnormality (found in 2-3% of live births) i.e. major organ system defect
- Developmental delay/intellectual disability
- Family history of genetic or syndromic disorders
- ≥3 minor anomalies:
    - 1 minor anomaly is found in ~15% of neonates e.g. clinodactyly, hypertelorism, epicanthic folds, syndactyly
    - These "differences" have no medical implications but may be indicative of other abnormalities

DOWN SYNDROME

Down syndrome (also known as Trisomy 21) is the most common genetic syndrome, occurring in approximately 1 in 600 live births. Although an individual woman's risk of having a child with Down syndrome increases with age (particularly after 35), anyone at any age can have a child with Down syndrome. There are several screening tests, including blood tests and ultrasound scans, that are available to determine the risk of aneuploidy (an abnormal chromosome number) in a pregnancy. How these are applied depends partly on local resources. Women with a child with Down syndrome are at greater risk of having another child with aneuploidy and should be offered referral for appropriate counselling before they become pregnant again.

Aetiology

Down syndrome is caused by the presence of three copies of chromosome 21, usually due to an additional chromosome 21 not joined to any other chromosome (non-disjunction).

3–4% of cases are caused by a translocation (14/21 or 21/21). Parents of these children may carry a balanced translocation, which is why their family members are at higher risk for having more children with Down syndrome. The risk in these

families is independent of maternal age and is the reason why chromosome analysis is important.

About 2% of people with Down syndrome have mosaicism (there are two cell lines in the same zygote – some somatic cells contain the extra chromosome, with visual examples accessible on this link, and some do not).

Clinical Features

There are no distinct diagnostic dysmorphic features, but the overall pattern of recognisable features in the setting of hypotonia and developmental delay assists with diagnosis. On physical examination, one should look for:

- Brachycephaly
- Upslanted palpebral fissures
- Brushfield spots (in the iris)
- Epicanthic folds
- Flat nasal bridge
- Low set ears
- Protruding tongue
- Loose neck skin
- Short, broad hands and fingers
- Short stature
- Clinodactyly
- Single palmar crease
- Sandal gap

See related image here.

Systemic involvement is common, and the child may have:

- Cardiorespiratory manifestations:
    - ~50% of patients have congenital heart disease, especially atrioventricular septal defects (AVSDs). They may also have patent ductus arteriosus (PDA), ventricular septal defects (VSD) or tetralogy of Fallot (TOF).
    - Recurrent wheeze and frequent chest infections (increased morbidity) are also common.
- Hearing and vision problems:

    - The child may have a congenital cataract (thus, one must always check the red reflexes) or strabismus.
    - 80% of patients have ophthalmologic disorders by 12 years old (myopia is most common).
    - Hearing loss is present in 40–70% of patients (may be sensorineural, conductive or mixed).
- Neurological manifestations:
    - Developmental delay and some impaired cognitive function is universal in children with Down syndrome (moderate intellectual disability is most common – the reported IQ range is 25–70).
    - These children have better receptive language than expressive language.
    - Seizures and epilepsy are present in 8% of patients. One must look for infantile spasms.
    - Autism spectrum disorder (ASD) is present in 8–12% of patients.
    - Cervical spine instability can cause cord compression.
    - Alzheimer-type dementia develops in 20–25% of people with Down syndrome who are >40 years old. A late decline in cognition is also common.
- Endocrine manifestations:
    - Thyroid dysfunction is present in 15% of people. Thus, thyroid function should be checked throughout the patient's lifespan as thyroid dysfunction can contribute to many co-morbidities.
    - Diabetes (type 1 or 2) and obesity are also common. The patient and family should be given lifestyle advice early on.
- Gastrointestinal manifestations:
    - Structural defects (e.g. duodenal atresia, Hirschsprung disease) are present in 12% of patients.
    - Umbilical hernia and coeliac disease may also be present.
- Haematological manifestations:
    - Myelodysplasia is present in 10% of neonates with Down syndrome.
    - The risk of leukaemia is 15–20-fold higher in the individual with Down syndrome (2% risk of acute lymphoblastic leukaemia).
- Autoimmune disorders:

    - As mentioned above, these children are more likely to develop type 1 diabetes and coeliac disease (4–15%).
    - Other common autoimmune disorders in these patients include idiopathic thrombocytopaenic purpura (ITP) and thyroiditis.
- Musculoskeletal and cutaneous manifestations:
    - Hypotonia and joint laxity are common
    - Eczema is also common

Initial Evaluation and Management

The initial evaluation of the child clinically diagnosed with Down syndrome often includes karyotyping, so that the diagnosis is certain and causes other than nondisjunction can be excluded for family counselling reasons. Surveillance for the commonly associated health complications and early developmental stimulation can substantially improve the long-term outcome for children with Down syndrome. Early assessment for congenital cardiac abnormalities clinically by chest X-ray and by ECG should be done in all children with Down syndrome, bearing in mind that a large AVSD will not always cause a heart murmur. An echocardiogram is recommended where available. If there is a serious cardiac abnormality, the baby will not thrive and will generally have other clinical signs of concern. Long-term monitoring of growth, vision, hearing and speech are important, as are periodic checks of thyroid function. Other care can be directed by clinical need.

OTHER TRISOMIES

Down syndrome (T21), Edward syndrome (T18) and Patau syndrome (T13) are the only trisomies compatible with life. T18 and T13 frequently result in death shortly after birth or in utero, but a small group of children (<5%) will survive to childhood. This is important to know when counselling expectant parents. These trisomies are also commonly due to nondisjunction, but can be caused by mosaicism or balanced translocation in a parent. Therefore, karyotyping is important to determine recurrence risk and implications for other family members.

Edward Syndrome (Trisomy 18)

Edward Syndrome occurs in ~1 in 6 000–8 000 births. Clinical features of T18 include:

- Small for gestational age infant
- Congenital heart disease (>80%)
- Neural tube defects.
- Diaphragmatic hernia/omphalocele
- Overlapping fingers
- Rocker bottom feet/clubfoot
- Micrognathia
- Small mouth (microstomia)
- Low set ears
- Prominent occiput

Some visuals associated with T18 features are accessible online via this link.

Patau Syndrome (Trisomy 13)

It occurs in ~1 in 8 000–12 000 live births. Clinical features of T13 include:

- Holoprosencephaly sequence (60–70% of cases) – hypertelorism, cutis aplasia, low set ears, sloped forehead (however, holoprosencephaly can also be caused by other chromosomal abnormalities, single gene disorders or teratogenic disorders)
- Microphthalmia/anophthalmia (60-70% of cases)
- Congenital cardiac disease (80% of cases, especially ASD or VSD)
- Enlarged kidneys and/or kidney malformations
- Cleft lip/palate (especially when central; can be associated with other midline defects – check for hypoglycaemia, electrolyte abnormalities, pituitary dysfunction)
- Absent eyebrows
- Dysplastic ears
- Clenched hands/ulnar deviation of overriding fingers
- Postaxial polydactyly (60-70% of cases)
- Omphalocele

Visuals related to some facial features in T13 are available here.

SEX CHROMOSOME DISORDERS

Klinefelter Syndrome

Klinefelter syndrome (47XXY) occurs in phenotypic males and has an incidence of ~1 in 600 (see examples of 47XXY features here). Affected individuals are tall and have hypogonadism (are usually infertile). They may also have learning difficulties, gynaecomastia, hypotonia and low muscle mass. It is difficult to detect in childhood although 1/3 of patients may have undescended testes. There are other health associations of which one should be aware.

Turner Syndrome

Turner syndrome is most often associated with a 45X0 karyotype and these children often have high rates of mosaicism. These children are phenotypically female but should have a PCR test done to look for Y chromosomal material, as its presence can indicate a higher risk of gonadoblastoma. See an example of preoperative webbed neck in Turner syndrome available here.

Prenatally, hydrops fetalis is common. Children may present early with puffy feet and webbing of the neck or at preschool age with short stature. Ovarian dysgenesis can present as delayed puberty or infertility.

There are some associated health complications, including congenital cardiac diseases (e.g. coarctation of the aorta, ASD, VSD, bicuspid aortic valve), renal abnormalities, mild learning difficulties (especially spatial/perceptual skills), hearing loss and hypothyroidism. However, intellect is usually normal.

FOETAL ALCOHOL SPECTRUM DISORDER (FASD)

FASD is a spectrum of disorders, including alcohol-related birth defects (ARBDs), alcohol-related neurodevelopmental disorders (ARNDs), foetal alcohol syndrome (FAS) and partial foetal alcohol syndrome (PFAS). No amount of alcohol at any stage of pregnancy is safe.

Between 1 in 5 and 1 in 100 children in some parts of South Africa are affected, depending on the social setting. It is more common in communities where there is

poverty, low maternal education, high unemployment rates and heavy or binge drinking.

Mechanism

Alcohol is a teratogen that crosses the placenta and interferes with the normal growth and development of the foetus. As with all teratogens, the outcome is related to the timing of exposure in gestation, the quantity of exposure and the duration of exposure. The outcome will be influenced by additional environmental factors. The most damage occurs in the embryogenic period, during the first 10 weeks after conception. However, alcohol can cause adverse neurological effects throughout pregnancy.

Clinical Features

Clinical manifestations depend, in part, on the stage of pregnancy in which the embryo or foetus was exposed to alcohol. For example, the characteristic facial appearance is due to drinking between weeks 4 and 10 of gestation. A visual of a baby with alcohol syndrome is available here.

One should suspect FASD in children with combinations of the following:

- History of significant history maternal drinking during pregnancy
- Characteristic facies with 2 or more of the following features:
    - Short palpebral fissures
    - Smooth philtrum
    - Thin vermillion border
- Pre- and postnatal growth deficiency
- Neurobehavioural abnormalities:
    - Microcephaly
    - Developmental delay
    - Attention deficit hyperactivity disorder (ADHD)
- Structural congenital malformations (not in all):
    - Congenital heart defects (especially VSD and ASD)
    - Structural renal abnormalities
    - Radioulnar synostosis and vertebral abnormalities

SHORT, DYSMORPHIC CHILDREN

For children with short stature (remember to calculate a mid-parental height), one should determine whether they have normal body proportions. Those that are disproportionately short in the trunk or limbs have a high likelihood of skeletal dysplasia and skeletal radiography can be helpful. A short trunk usually implies spinal involvement and is seen in conditions like spondyloepiphyseal dysplasia and mucopolysaccharidoses. The most common skeletal dysplasia is achondroplasia, in which children present with disproportionately short limbs. Height abnormalities will be more extensively covered in the endocrine section.

Achondroplasia

Achondroplasia occurs in ~1 in 15 000–40 000 neonates. It is an autosomal dominant condition, although most cases are the result of a new mutation. Individuals who inherit two copies of the mutation have such severe achondroplasia that they are stillborn or die soon after birth. Phenotypically, individuals with achondroplasia are short (average male = 131 cm and female = 124 cm) with rhizomelic shortening of arms and legs (the proximal limb segments are most affected – humerus and femur – see also image here), relative macrocephaly with prominent foreheads and short fingers with a gap between the 2nd and 3rd digits (trident hands).

Children with achondroplasia have low tone and joint laxity. They are prone to:

- Upper airway obstruction (both central and obstructive apnoea)
- Obesity
- Ear infections
- Skeletal problems e.g. infantile kyphosis (usually resolves), lumbar lordosis, tibial bowing, spinal stenosis (later in life)

Macrocephaly is inevitable but true hydrocephalus is rare. There is always a narrow craniocervical junction and infants in particular should be closely monitored for any neurological abnormalities and referral for imaging should be considered. Growth should be plotted on an achondroplasia growth chart. Careful attention should be given to supporting the relatively heavy head in infancy and avoiding overextension or flexion of the neck.

OTHER GENETIC SYNDROMES AND DISORDERS

Neurocutaneous Disorders

They include:

- Neurofibromatosis:
    - It is an autosomal dominant condition.
    - Clinical features include Lisch nodules, axillary and inguinal freckling, café au lait spots, scoliosis and neurofibromas.
    - These children have an increased risk of learning difficulties and tumour risk.
- Tuberous sclerosis:
    - It is an autosomal dominant condition associated with CNS astrocytomas, renal angiomyolipomas and cardiac rhabdomyomas.
    - Clinical features include intellectual disability, autism, epilepsy (particularly infantile spasms), hypopigmented macules, facial angiofibromas, periungual fibromas and shagreen patches.
- Sturge-Weber syndrome:
    - It is a sporadic condition that is caused by mosaicism.
    - Clinical features include port wine stains/haemangiomas in the V1 distribution, hemiplegia and epilepsy (especially focal epilepsy).

Neuromuscular Disorders

They include:

- Spinal muscular atrophy:
    - The clinical severity of this autosomal recessive disease varies.
    - Patients will have lower motor neuron signs (fasciculations, areflexia, muscle wasting and muscle weakness that eventually involves the respiratory muscles).
- Duchenne's muscular dystrophy:
    - It is an X-linked recessive condition, so males are mostly affected.
    - The child will have proximal muscle weakness (Gowers's sign) with calf pseudohypertrophy. The weakness is progressive with eventual cardiac and respiratory involvement. Duchenne's muscular dystrophy is also associated with cardiomyopathy.

Additional Autosomal Recessive Disorders

These disorders may not be apparent in family history because they are recessive (both copies of the gene must be abnormal for disease to manifest). Most metabolic conditions and many causes of hearing and vision loss are autosomal recessive.

Sickle Cell Disease/Anaemia
In this condition, red blood cells have a sickle shape and haemoglobin has abnormal oxygen-carrying capacity of haemoglobin. Patients may present with pain crises, stroke or severe anaemia. Sickle cell anaemia is common in sub-Saharan Africa and other areas where malaria is prevalent.

Cystic Fibrosis
It is the result of a defect in the cystic fibrosis transmembrane conductance regulator (CFTR), resulting in thick secretions. This multisystemic disorder causes:

- Salty skin
- Pancreatic insufficiency and malabsorption (with resultant poor growth)
- Recurrent chest infections (can lead to chronic lung disease)
- Bowel obstruction (meconium ileus)

It is more common in those of European ancestry but occurs in all ethnicities.
Examples of red blood cells and sickle cells are accessible here.

Conditions Presenting with Developmental Delay and Intellectual Disability

Fragile X Syndrome
It is an X-linked condition, thus males are more severely affected. Females are protected by skewed inactivation and usually have milder symptoms. Children present with delayed milestones (particularly delayed speech at 2 years), hyperactive behaviour, mild-to-moderate intellectual disability and ASD. Physical features may include a long and narrow face, prominent forehead, large jaw, large ears and joint laxity.

Velocardiofacial Syndrome/DiGeorge Syndrome (22q11.2 Deletion Syndrome)
It is caused by a microdeletion of chromosome 22. Clinical features include:

- Cleft palate
- Thymic and parathyroid gland hypoplasia (present with hypocalcaemia)
- Congenital cardiac disease e.g. truncus arteriosus (usually caused by 22qdel), VSD and tetralogy of Fallot (75%)
- GORD
- Learning disabilities
- Tapered fingers
- Midface hypoplasia
- Deficient alae nasae
- Poorly developed upper helices of the ears

Psychiatric comorbidities (schizophrenia, bipolar mood disorder) may develop later on in some.

Prader-Willi Syndrome

It is an imprinting disorder that usually occurs in the absence of a family history. Patients often present in infancy with hypotonia and low birth weight or later on with insatiable hunger and obesity. Thus, food control is essential.

Prader-Willi syndrome is associated with delayed milestones, hypotonia, narrow forehead, small hands and feet. These children are prone to endocrine abnormalities including hypogonadism, hypocortisolism and hypothyroidism.

Pierre-Robin Sequence

A sequence is a series of sequential developmental effects. In this case, the primary abnormality is underdevelopment of the jaw which leads to displacement of the tongue posteriorly and can cause a cleft palate. This results in problems in early life including upper airway obstruction, feeding difficulties and failure to thrive (FTT). It may be isolated or part of a genetic syndrome.

Other Syndromes to Recognise

Alagille Syndrome

It is an autosomal syndrome condition in which there is intrahepatic bile duct paucity. The child will present with prolonged neonatal jaundice, cholestasis and pale stools. Other features include cardiac disease (VSD, pulmonary valve stenosis), skeletal

abnormalities (butterfly vertebrae), ocular abnormalities and typical facies (deep set eyes, pointed chin).

Peutz-Jeghers Syndrome

It is an autosomal dominant syndrome in which children have gastrointestinal polyps (may present with intussusception), hyper-pigmented mucosae and freckles on the face, hands, feet and digits. It is associated with early-onset cancers in adulthood especially GI, breast and pancreatic cancers.

Beckwith-Wiedemann Syndrome

It is an overgrowth syndrome with clinical features of macrosomia at birth, neonatal hypoglycaemia, macroglossia, midline abdominal defects and ear creases/pits. It is associated with an increased risk of embryonal tumours, including Wilms tumour and hepatoblastoma.

GENETIC TESTING

Genetic testing can be done for different reasons and the technique chosen will depend on the question being asked and the disorder in question. It is important to liaise with a geneticist and the laboratory to ensure you choose the best test for the situation and that you are aware of the limitations of that test.

Types of Genetic Tests

The genetic test may be:

- Diagnostic (to confirm a clinical diagnosis).
- Predictive (to provide information about future risk or disease; generally not advised in childhood unless a preventive intervention is available).
- Carrier (to check whether an individual carries a genetic variant that will have reproductive implications).

See related image here.

Genetic Test Results

As there is so much interindividual variability, it can be difficult to know if a genetic variant found on a test is the cause of a problem or not. This means there are three possible results from a genetic test:

- Positive – a pathogenic or likely pathogenic variant has been found.
- Negative – no variant or a benign variant has been found.
- Variant of uncertain significance (VUS) – at this stage, there is insufficient evidence to decide if the variant detected causes a problem or not (effectively also a negative result as one cannot use this result to make clinical decisions).

As more genes are tested (what with testing of the whole exome or whole genome), VUS is becoming a more frequent result (particularly in African populations, which are not well represented in datasets). Thus it is important to understand the concept of VUS. One must remember that information is rapidly being produced and variants may be reclassified in time. A genetic counsellor can help with the interpretation of test results and with communicating genetic information to patients.