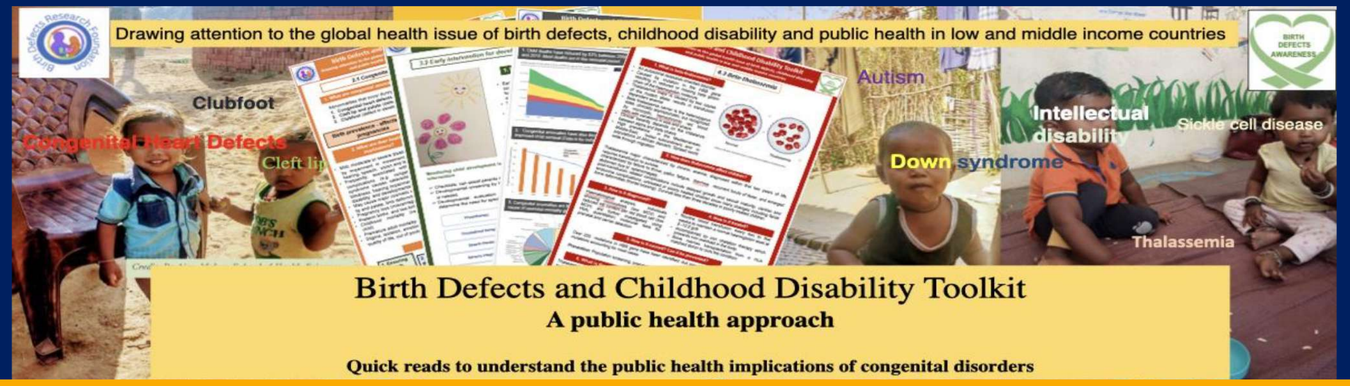

Birth Defects and Childhood Disability Toolkit

Section 4 - Some common genetic disorders

Birth Defects Research Foundation, Pune, India

A research NGO working for evidence based policies and advocating for the rights of children with disabilities caused by congenital, developmental and genetic disorders

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4.1 Public health issues of genetic disorders in LMICs

- Genetic disorders are inherited conditions, caused by a pathogenic variant in a gene encoding an essential protein in the body
- The table shows some examples :

Disorder	Gene	Affected protein	Affected function
Sickle cell disease	HBB	Haemoglobin Subunit Beta (Beta globin chain of haemoglobin)	Haemoglobin synthesis
Beta-thalassemia	HBB	Haemoglobin Subunit Beta (Beta globin chain of haemoglobin)	Haemoglobin synthesis
Haemophiila A	F8	Coagulation Factor VIII	Blood coagulation
Haemophiila B	F9	Coagulation factor IX	Blood coagulation
Muscular dystrophy	DMD	Dystrophin	Muscle structure
Achondroplasia	FGFR3	Fibroblast Growth Factor Receptor 3	Impaired growth of bones

- Some genetic disorders are common and constitute important public health problems
- Genetic disorders are characterized by the fact that they are life-long (chronic), life-limiting (life expectancy is lower, more so when there is no treatment) and life-threatening (frequent need for emergency hospitalization)
- Most disorders cause premature mortality, but for some conditions (like haemophilia), replacement therapy can improve life expectancy to that of the general population
- As lifelong conditions, caregivers have to deal with living with the disorder
- This includes emotional adjustments as disorders progressively deteriorate, there is progressive disability and medical complications, leading to early mortality

Key public health issues are:

Developing genetic services :

1. Identifying prevalent conditions requiring public health interventions
2. Developing specialist referral centres for management of patients by Identifying specialists for developing capacity and skills of health staff developing infrastructure and consumables
3. Genetic counselling services
4. Establishing referral to rehabilitation services, such as for muscular dystrophy and haemophilia
5. Psychosocial support for children, adults and caregivers
6. Education of caregivers on home management, warning signs requiring hospitalization

Identification of patients :

7. Screening from high risk communities
8. Increasing awareness about the cardinal signs and symptoms of prevalent disorders among general practitioners, providing information on availability of the specialist genetics centres

Prevention :

9. Genetic counselling services

Surveillance :

10. Development of disease registers to identify the number and characteristics of patients

Collaborations :

11. Networking with non-governmental organizations for outreach and delivery of services

4.2 Sickle cell disease

1. What is SCD?

- Group of inherited, autosomal recessive genetic disorders, caused by mutation in the *HBB* gene encoding the beta subunit of haemoglobin
- A mutation in the HBB gene results in the sickle Hb (HbS) allele, β^S
- In low oxygen conditions, Red blood cells are **shaped like sickles or crescent moons due to polymerization of HbS**
- **RBCs are more prone to hemolysis, appear** rigid and sticky, which blocks small blood vessels, slowing down or blocking blood flow and oxygen to affected parts of the body
- Sickle cell disease (SCD) occurs when both *HBB* alleles are mutated
- Sickle cell trait is when one copy of HBB is a β^S allele

2. How does SCD affect children?

- Anemia
- Episodes of pain mainly in the long bones of the hands and feet, hip joint, back, toes, fingers,
- Pain may persist from a few hours to weeks,
- Painful swelling of abdomen, jaundice
- Repeated sudden onsets of infection
- Leg ulcers
- Affects major body organs, causing **comorbidities** like; pulmonary complications, heart failure, stroke, bone damage, seizures, kidney damage,

3. How is it diagnosed?

Laboratory tests - Hemoglobin electrophoresis

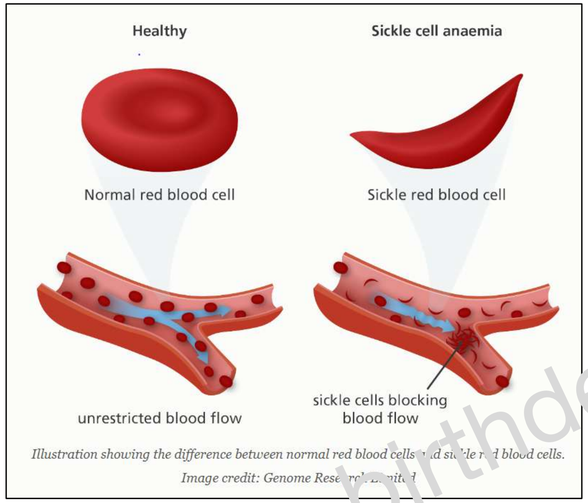


Illustration showing the difference between normal red blood cells and sickle red blood cells.
Image credit: Genome Research Limited

4. How is it treated?

Bone marrow transplant, treatment with hydroxyurea, folic acid; as necessary pain medications, antibiotics, blood transfusions, ensuring full immunizations, regular check ups

7. What is the public health role?

- Screening in high risk communities
- Genetic counselling
- Provision of medical care for sickle cell disease
- Psychosocial support

5. How is it caused? Can it be prevented?

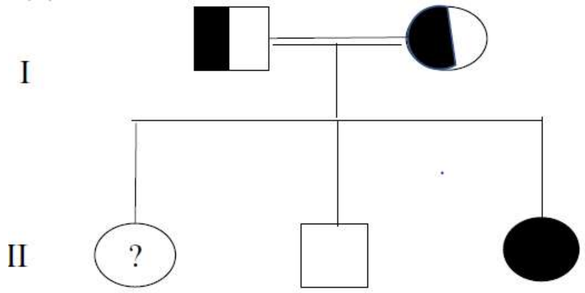
Caused by adenine-to-thymine substitution resulting in replacement of glutamic acid with valine at position 6 in the mature β-globin chain

- A person will be born with sickle cell disease only if two HbS alleles are inherited—one from each parent
- Sickle cell trait is when a person inherits one copy of HbS; individual is healthy but a "carrier" of the disease.
- Marriage between carriers increases the risk of an affected birth; each pregnancy has a 25% chance of being affected, and 50% chance of being a carrier.

Prevention
Genetic counselling

6. What is the recurrence risk?

Sickle cell anemia is inherited as an autosomal recessive trait. If parents are carriers there is a 25% risk of the child being affected and a 50% risk of the child being a carrier.



Autosomal recessive inheritance

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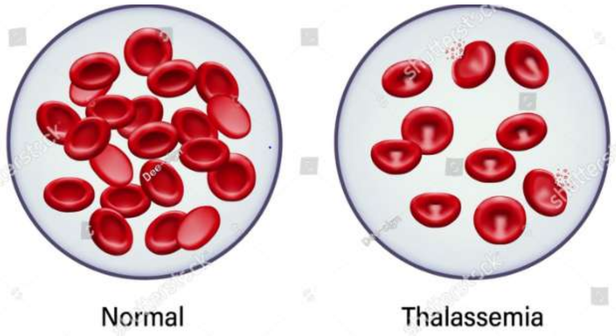
4.3 Beta-thalassemia

1. What is beta-thalassemia?

- An autosomal recessive inherited disorder
- Caused by mutation in the HBB gene resulting in reduced or missing beta globin chain of the haemoglobin molecule
- Thalassemia major is caused by two copies of the mutant allele; results in transfusion dependent anemia
- Beta thalassemia carrier is the heterozygous state, clinically asymptomatic, but recognized by microcytic, hemochromic red blood cells,with variations in size and shape
- Clinical severity depends on the imbalance between alpha and beta chains
- High prevalence in the Mediterranean, Middle-East, Indian subcontinent, and in populations of African descent. Spread world wide through migration

2. How does thalassemia affect children?

Thalassemia major characterized by chronic anemia, diagnosed within first two years of life, requires transfusion to survive, characterized by failure to thrive, pallor, fatigue, diarrhea, recurrent bouts of fever, and enlarged abdomen due to splenomegaly;
post-transfusion related complications include delayed growth and sexual maturity, cardiac and endocrine complications, untreated or poorly treated children show many changes including facial bone deformities (frontal bossing). Survival less than three decades in poorly treated children



3. How is it diagnosed?

Haematological analysis, individuals showing microcytosis (low MCV) and reduced Hb content per red blood cell (low MCH) are further investigated using HbA_2 quantitation; molecular tests for prenatal and carrier detection

4. How is it treated?

- Routine blood transfusion every two to five weeks to maintain a normal haemoglobin level at 9 -10.5 g/dl
- Accompanied by iron chelation therapy which prevents iron overload in the body
- Bone marrow transplantation from a HLA matched donor to cure the condition

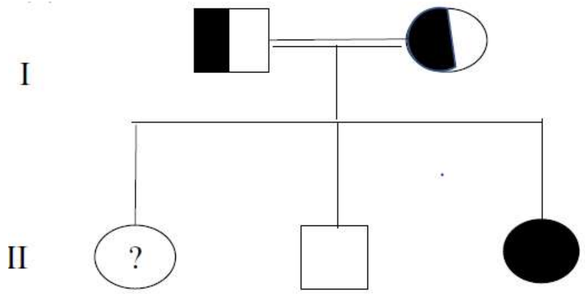
5. How is it caused? Can it be prevented?

Over 200 mutations in HBB gene have been identified; but populations have few predominant mutations accounting for most cases

Prevention: Population screening, prenatal diagnosis and Genetic counselling

6. What is the recurrence risk?

Thalassemia is inherited as an autosomal recessive trait. If parents are carriers there is a 25% risk of the child being affected and a 50% risk of the child being a carrier.



Autosomal recessive inheritance

7. What is the public health role?

- Screening in high risk communities
- Genetic counselling
- Provision of medical care for sickle cell disease
- Psychosocial support

References
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Birth Defects and Childhood Disability Toolkit

Drawing attention to the global health issue of birth defects, childhood disability and public health in low and middle income countries

4.4 Hemophilia

1. What is haemophilia?

- Inherited bleeding disorders affecting 1 in 5000 males, caused by missing or sub-optimal levels of clotting factor VIII (haemophilia A) or factor IX (haemophilia B) ,
- Severity of haemophilia depends on blood clotting factor levels
- **Severe haemophilia** (1% residual clotting factor activity) – characterized by repeated spontaneous bleeding episodes, as frequently as once a month
- **Severely moderate haemophilia** (1-5% residual clotting factor activity) - bleeding episodes related to trauma,
- **Mild haemophilia** (5-40% clotting factor activity) – unusual bleeding, usually identified at time of surgery , dental work
- The frequency of bleeding episodes is patient-specific

2. How does haemophilia affect children?

- Repeated, prolonged bleeding episodes accompanied by severe pain
- Cardinal signs are haematoma (bruises on skin due to bleeding in tissues), haemarthrosis (bleeding in joints), haematuria (blood in urine)
- Weight carrying joints (knee, ankle, hip, elbow) mostly affected, untreated bleeding manifests as haemarthrosis, swollen and very painful joints which limits mobility, and causes progressive joint disease and chronic pain
- Soft tissue bleeding, presents as bruising
- in babies, prolonged bleeding after tooth loss, bleeding at site of injection after immunization
- prolonged and frequent nose bleeds,
- Pain leads to loss of school days, immobility leads to progressive disability, restricted participation from activities that might cause trauma results in emotional issues,
- Intracranial bleeding manifesting as seizures, life threatening
- Severe bleeding without treatment can lead to early mortality

3. How is it diagnosed?

- Laboratory tests like Complete Blood Count (CBC), Activated Partial Thromboplastin Time(APTT), Prothrombin Time (PT) , and
- Factor Assays to determine the type and severity of haemophilia

4. How is it treated?

Replacement therapy through intravenous transfusion with clothing factor (clotting factor VIII for haemophilia A, or clotting factor IX for haemophilia B)

- This results in restoring clotting factor levels resulting in cessation of bleeding
- Access to clotting factor is limited by high costs, so that most patients in LMICs remain untreated

5. How is it caused?

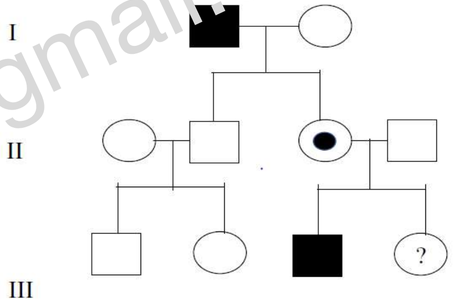
Haemophilia A is caused by a mutation in clotting factor VIII (F8) gene, haemophilia B is caused by a mutation in clotting factor IX (F9) gene

Access to optimal quantities of clotting factor concentrate can improve life expectancy to that of the general population

6.How is it inherited?

As a sex-linked recessive disorder, each son born to a woman carrying a dystrophin mutation has a 50% risk of inheriting the disorder.

Prevention is through genetic counselling **child being a carrier.**



X – linked recessive inheritance

7. What is the public health role?

- Major public health issue in LMICs is the lack of access to clotting factor concentrate
- Public health role is to
- Ensure access to required amounts of clotting factor concentrate ,
- medical services for complications, rehabilitation therapies, assistive devices when required
- Psychosocial support
- Provision of genetic counselling services
- Implementation of laws protecting rights and dignity
- Linking families to patient support groups
- Supporting NGOs providing services to patients and families

References

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Annual Global Survey (latest year) World Federation of Hemophilia -----

4.5 Muscular dystrophy

1. What is muscular dystrophy?

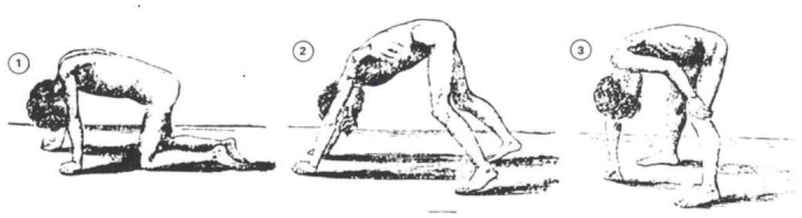

Fig. 2.8 Gowers' sign. From William Richard Gowers (1845–1915)—Gowers WR. Clinical lecture on pseudohypertrophic muscular paralysis. Lancet 1879; ii, 73–75

Group of genetic disorders affecting muscle development and function. Characterized by progressive weakness of muscles, and loss of muscle mass. Most common forms are

Duchene muscular dystrophy (DMD) – DMD develops by the age of 2-3 years of age. Progressive muscle wasting and weakness due to degeneration of skeletal, smooth and cardiac muscles. Median life expectancy with ventilatory support ranges between 21.0 and 39.6 years

Becker muscular dystrophy (BMD) – BMD is a milder form of muscular dystrophy with a slow progression, so that children develop the condition by adolescence. Signs similar to DMD. Average life expectancy 40-50 years

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Crisafulli, S et al (2020). Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet journal of rare diseases*, *15*(1), 1-20.
Landfeldt (2020). Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *European journal of epidemiology*, *35*(7), 643.

2. How does muscular dystrophy affect children?

- Difficulty in walking, running, rising from the floor, from lying or sitting position or climbing stairs. Children rise up taking support in a specific manner (Gower's sign).
- Trouble running and jumping, wadding gait, walking on toes,
- hypertrophy of calf muscles,
- Muscle pain, stiffness, frequent falls
- Delayed growth, learning disabilities
- Premature mortality related to cardiac and respiratory complications

3. How is it diagnosed?

- Laboratory tests to identify creatine kinase levels (increases if there is muscle damage in the body)
- Muscle biopsy
- Genetic testing

4. How is it treated?

Symptomatic treatment, rehabilitation therapies to prolong mobility , cardiac and respiratory care

5. How is it caused?

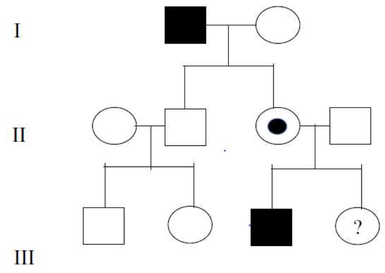
Caused by a mutation in the dystrophin gene. Dystrophin is a cytoskeletal protein found mainly in skeletal and cardiac muscles

6. How is it inherited ? What is the recurrence risk? Can it be prevented?

As a sex-linked recessive disorder each son born to a woman carrying a dystrophin mutation has a 50% risk of inheriting the disorder. Prevention is through genetic counselling

Recurrence risk of 14% for brothers of sporadic cases with the same haplotype when the mutation could not be detected

Prevention through genetic counselling



DMD X – linked recessive inheritance

7. What is the public health role?

- Provision of genetic counselling services
- medical services, rehabilitation therapies, assistive devices
- Psychosocial support for children and adults
- Support to caregivers
- Implementation of laws protecting rights and dignity of people with disabilities
- Linking families to patient support groups
- Supporting NGOs providing services

4.6 Achondroplasia (Dwarfism)

1. What is achondroplasia?

- Unusually short stature (131 5.6 cm, i.e. 4 feet 10 inches) or less for men, (124 5.9 cm, 4 feet) or less for women
- Disproportionately short arms and legs
- Larger head size, middle part of the face is not well developed, nasal bridge not well formed
- Short chubby hands with a space between third and fourth fingers
- Lordosis of the spine (spine is abnormally flexed), small chest, protruding abdomen, enlarged buttocks
- Bowed legs

https://depositphotos.com/.../stock-illustration-dwarfism.html

2. How does dwarfism affect children? adults ?

- Delayed motor milestones, hypotonia, speech delay, hydrocephalus
- Repeated ear infections, increased risk of hearing loss
- Dental issues due to misaligned teeth,
- Stiff elbows, limited ability to straighten arms
- Kyphosis, bent spine, bowed legs, causing gait problems chronic back and leg pain,
- Obstructive sleep apnea,
- Obesity, increased risk of high blood pressure
- Psychological issues like depression and low self – esteem

3. How is it diagnosed?

Detected in ultrasound scan by the third trimester of pregnancy identifiable as short limbs and depressed nasal bridge

4. How is it treated?

No cure for dwarfism, symptomatic treatment of complications and comorbidities,

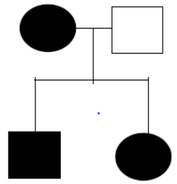
- In certain cases; growth hormone treatment, leg-lengthening treatments

5. How is it caused?

Genetic condition, caused by mutation in FGFR3 gene

6. How is it inherited ? What is the recurrence risk? Can it be prevented?

- Transmitted in autosomal dominant manner (transmitted either from father or the mother)
- Nearly 80% of children with short stature have parents of usual height
- Increased father's age is a risk factor
- **Recurrence risk** of achondroplasia in the siblings of achondroplastic children with unaffected parents estimated as **1 in 243 (0.2%)**
- **Prevention** through genetic counselling



Autosomal dominant mode of transmission

7. What is the public health role?

- Provision of genetic counselling services,
- medical services, rehabilitation therapies, assistive devices as required,
- Psychosocial support for children and adults,
- Support to caregivers,
- Implementation of laws protecting rights and dignity of people with achondroplasia,
- Linking families to patient support groups
- Supporting NGOs providing services

References

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