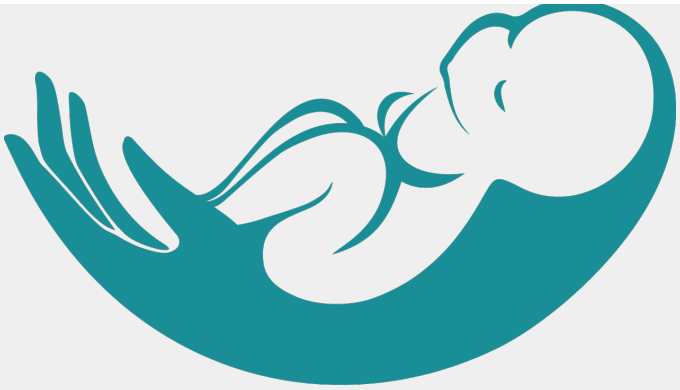


435 PEDIATRICS

Metabolic Disorders

Dr. AlOmair

Objectives:
Focusing on the 3 Most Common

- Understand the types, etiology and pathophysiology of metabolic disorders/inborn errors of metabolism.
- Understand the role of genetics in metabolic disorders/inborn errors of metabolism.
- Understand the general principles in clinical features and methods of detection of metabolic disorders.
- Understand the clinical presentation of metabolic disorders/inborn errors of metabolism.
- Understand the spectrum of metabolic disorders and the basic principles in management.

Done by:
Aya Ghanim

References:
Doctor's slides + notes

This only includes what the doctor mentioned/focused on. For additional info, see 431 or Illustrated.

Color index: [important | notes | extra]

Overview

- **Effects of metabolic disorders:**
  - Toxic accumulation of substrates before the block. Best example of this is galactosemia (which is caused by an enzyme deficiency leading to abnormal accumulation of galactose in the body). Or PKU (phenylalanine accumulates in the body due to deficiency of phenylalanine hydroxylase)
  - Intermediates from alternative pathways. They are chemical products before the end product. Intermediate products may be **harmful.**
  - Defects in energy production (result of many metabolic enzyme disorders which make glucose and other nutritional factors unavailable in the cell) and utilization caused by a deficiency of products beyond the block. Considered a secondary result of the metabolic disorder.
  - Note:
    - There may be a combination of metabolic deviations. E.g. Accumulation AND lack of energy occur in glycogen storage diseases.
    - CNS is first to be affected from a symptomatology point of view.

- **Incidence:**
  - Incidence of inborn errors of metabolism as a whole is estimated to be 1/800 live births. We should be careful with those figures since they are often derived from western references and textbooks. Real incidence in Saudi Arabia or the Middle East in general may be higher b/c of consanguineous marriages.
  - Incidence of each inborn error of metabolism is individually rare.
  - **PKU**: 1/10,000 live births. The incidence of PKU is much lower in Saudi Arabia. We see more galactosemia and **CONGENITAL HEREDITARY HYPOTHYROIDISM**.
  - **Galactosemia:** 1/40,000-60,000 live births.
  - Incidence within different racial and ethnic groups varies with predominance of certain inborn errors:
    - **Cystic Fibrosis**: 1/1600 people from a European descent. Cystic Fibrosis (CF) is an autosomal recessive disease, meaning both parents need to be heterozygous (carriers) and 25% of their offspring will be homozygous (i.e. will have CF)
    - **Sickle Cell Anemia**: 1/600 people from an African descent. (including Africans in other countries e.g. African Americans)
    - **Tay-Sachs** (lipid storage disease): 1/3500 in Ashkenazi Jews.
    - Also Thalassemia in Greece & Italy.

- **Importance?** Causes morbidity: handicap, pain, disorder, mental retardation, etc. & sometimes mortality

- **Prognosis:**
  - Prognosis depends on speed of diagnosis. Example: Saudi baby in the nursery, with a drop of blood is discovered to have **congenital hereditary hypothyroidism**. Both parents heterozygous and the baby is homozygous (it's autosomal recessive). Once you treat the baby in the nursery with thyroxine > they grow up normally.
  - Even babies with galactosemia are discovered with jaundice in first week of life in nursery and if you remove galactose completely from their diet for life **"galactose-free milk/diet"** > they recover and grow normally.
  - In PKU, you can't give them a phenylalanine-free diet, because phenylalanine is an essential amino acid. So instead you them **"phenylalanine-low milk/diet".**

- **Suggestive of metabolic disorder:**
  - **History:** Consanguineous marriage (first or second degree), unexplained death of a previous baby, particular ethnic group (e.g. Ash Jew)
  - **Examination:** Organomegaly, cardiac disease, ocular involvement (e.g. cherry red spot), skin manifestations e.g. pigmentations, unusual odor, non-specific neurological findings.

✻ **Neonatal & Post-natal Presentation:**

- **Neonatal:** (Can present with problems at birth or first feed like galactosemia or PKU "within the first week" or would take more time to appear)
  - **Poor feeding**
  - **Lethargy**
  - **Vomiting**
  - **Seizures**
  - **Coma**
  - **Unusual odor** (or acidic smell like in PKU)
  - **Hypoglycemia** or acidosis on blood gases)

  Problem is all those signs can come with neonatal infection as well
- **Post neonatal:** (anything after 35-40 days of life)
  - **Encephalopathy** not interacting with parents, irritable, poor feeding, goes to sleep easily, less energy, sick-looking
  - **Developmental regression** in those 3 months and older. E.g. used to sit at 6 months but now at 10 months falls over
  - **Reye Syndrome** (hepatomegaly, encephalopathy) rare but serious condition that causes swelling in the liver and brain. Famous **aspirin** complication.
  - **Motor deficit** can be hyper or hypotonia
  - **Seizures** out of the blue > not caused by infection "not a febrile seizure"
  - **Intermittent episodes of vomiting, acidosis, hypoglycemia and/or coma triggered by stress e.g. infections, surgery.**

✻ **Newborn Screening:**

- **PKU - in NICU even if not advanced to full feeds**
- **Galactosemia**
- **Hypothyroidism** very important in KSA
- **Hemoglobinopathies**
- **Biotinidase deficiency CAH (21-OH'ase def)**
- **Maple syrup urine disease (MSUD)**
- **GUTHRIE TEST: it's a cheap test that requires only one drop of blood to check for multiple metabolic disorders.**

✻ **Diagnosis:**

- A simple test would be bedside ketones. Presence of ketosis or acidosis (especially high anion gap) > there is a problem. E.g. organic acidemia.

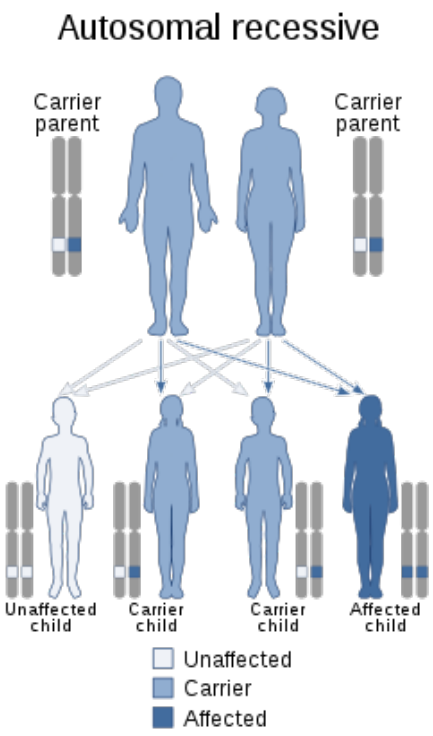
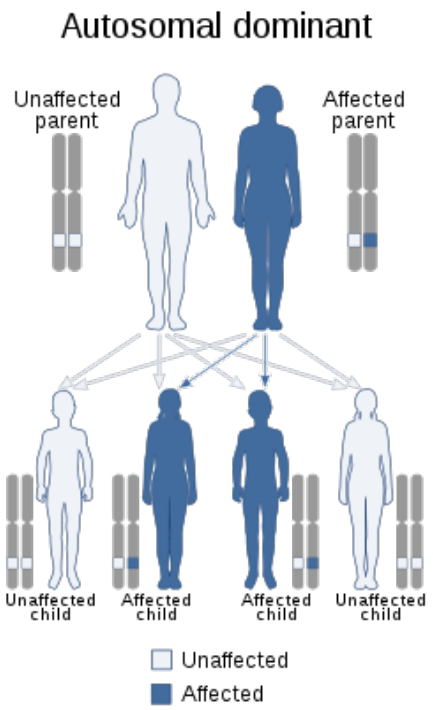
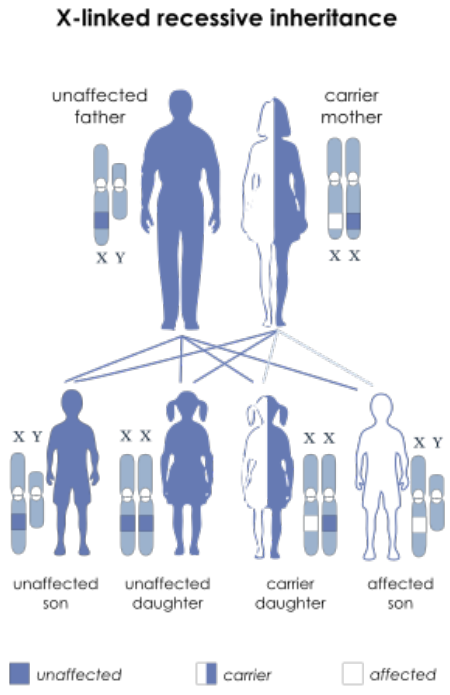
✻ **Treatment:**

- Depends on the disorder. There is a specific treatment for each of them.
- Both short and long-term management depend on the underlying diagnosis.
- Immediate emergency management is based on removing toxic metabolites from the body.
- Most times need a transfer to the NICU.
- Some might need mechanical ventilation due to severe metabolic disruption or hemodialysis to clear the blood from harmful metabolites.
- **E.g. Skilled dietetic support**. "gluten free diet"**, Specific med** e.g. thyroxine

✻ **Inborn errors of amino acid metabolism are associated with abnormal odor in urine, sweat, and tears:**

Inborn Error of Metabolism	Urine Odor
Gultaric Acidemia	Sweaty feet
Maple Syrup urine disease	Maple Syrup
Hypermethioninemia	Boiled Cabbage
Phenylketonuria	Mousy or musty
Trimethylaminuria	Rotten fish

✻ Types of Inheritance:

Autosomal Recessive	Autosomal Dominant	X-linked
25% of offspring of unaffected carrier parents	50% of offspring of one affected parent	Normal father, carrier mother > affected male child
✻ Congenital Adrenal Hyperplasia Most important problem is ambiguous genitalia. ✻ Cystic Fibrosis ✻ Friedreich's Ataxia ✻ Galactosemia ✻ Glycogen Storage Disease ✻ Hurler Syndrome (Mucopolysacchridosis I) ✻ Oculocutaneous Albinism ✻ Phenylketonuria ✻ Sickle Cell Disease ✻ Tay-Sach's Disease ✻ Thalassemia ✻ Werdnig Hoffmann disease	✻ Achondroplasia ✻ Ehlers-Danlos Syndrome ✻ Familial Hypercholesterolemia ✻ Huntington's Disease ✻ **Marfan Syndrome** ✻ Myotonic Dystrophy ✻ Neurofibromatosis ✻ Noonan's Syndrome ✻ Osteogenesis Imperfecta ✻ Tuberous Sclerosis	✻ Color-blindness ✻ DMD (Duchenne Muscular Dystrophy) & Becker ✻ Fragile X Syndrome ✻ G6PD urine cola color, low hemoglobin, and jaundice when eating beans ✻ Hemophilia A & B ✻ Hunter's Syndrome (Mucopolysacchridosis II)
		

Dysmorphologies

* **Definition:** The malformation seen visibly on the face, neck, extremities, chest, eyes, fingers and toes etc.

* **Down Syndrome (Trisomy 21):** Incidence is higher in ladies above 45 years of age (1/30 babies)
  - **Epicanthal folds** prominent
  - **Slanting eyes** not completely horizontal, slants upwards
  - **Depressed nasal bridge**
  - **Low set ears**
  - **Sandal gap**
  - **Single Palmar Crease** sometimes normal
  - **Brushfield spot**
  - **Brachycephaly** Flat occiput

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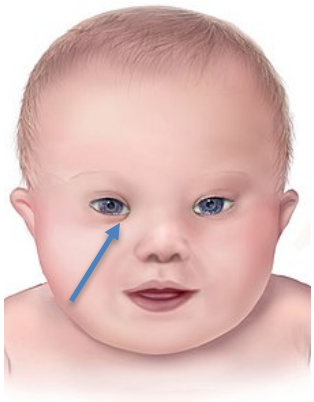	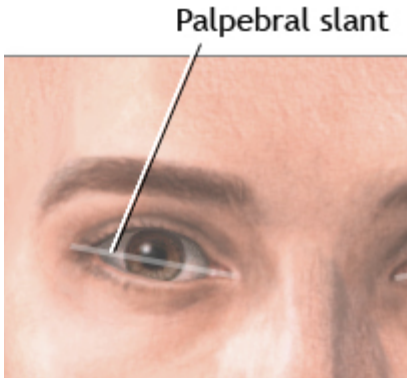		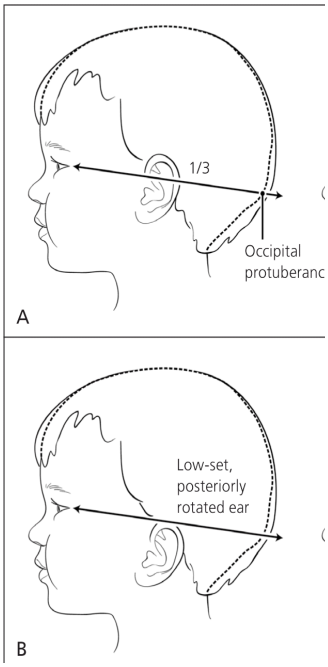
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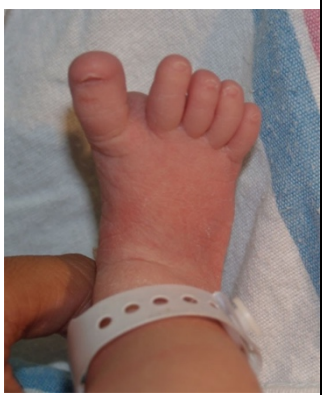			

✻ Hurler's Syndrome: Mucopolysacchridosis I, RECESSIVE

1. **Corneal Clouding**
2. **Depressed nasal bridge**
3. **Upturned nostrils**
4. **Macroglossia** large tongue
5. **Excessive epicanthal folds**
6. **Long philtrum**
7. **Umbilical Hernia**
8. **Hepatosplenomegaly**
9. **Abdominal Distension**
10. **Kyphosis**
11. **Short stubby fingers**
12. **Pectus Carinatum AKA Pigeon chest** because of cardiomyopathy "heaving heart"

Note: Unlike Hurler's syndrome which is autosomal recessive with corneal clouding, Hunter's Syndrome (Mucopolysacchridosis II) has X-linked inheritance and NO CORENEAL CLOUDING.

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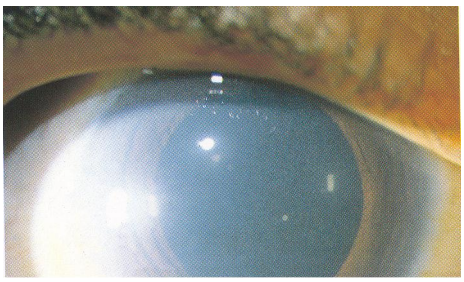
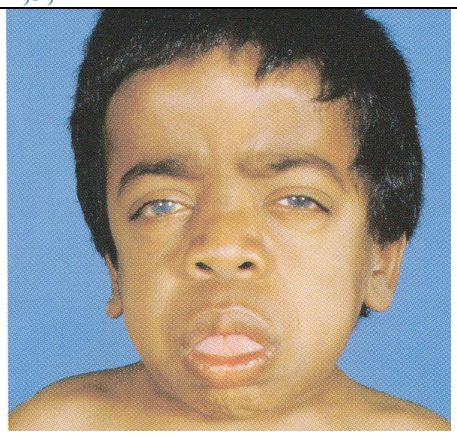
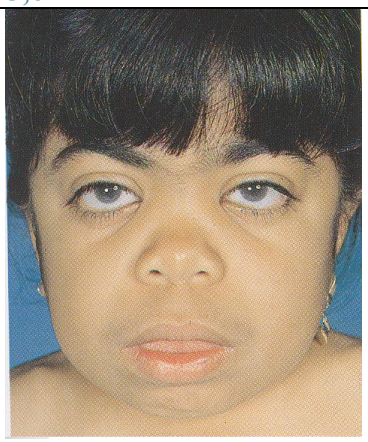
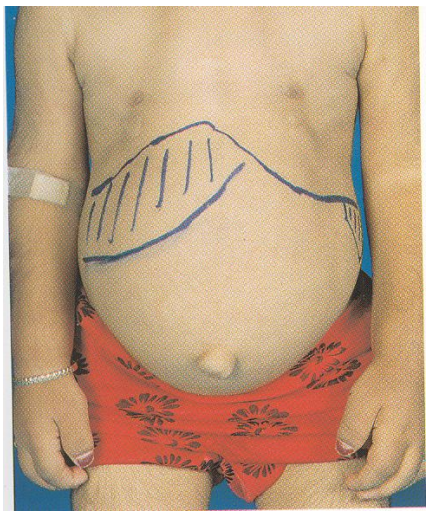
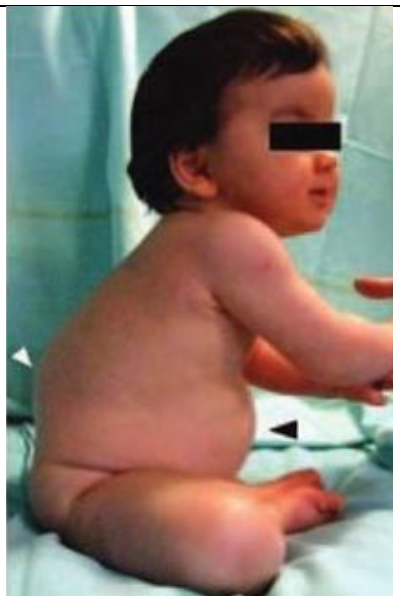
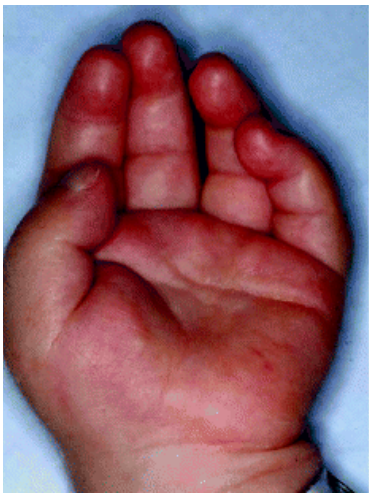
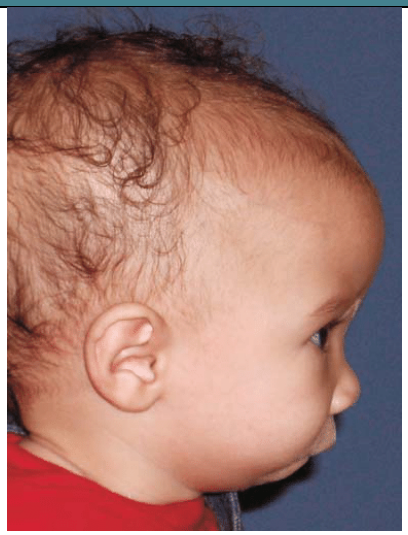
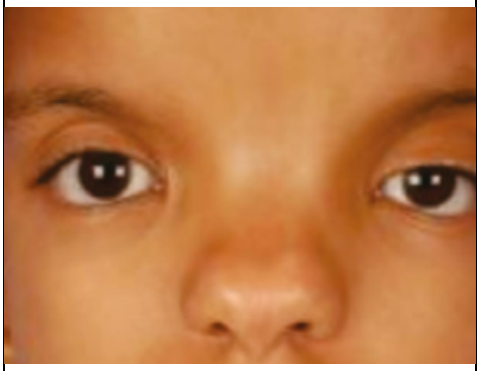
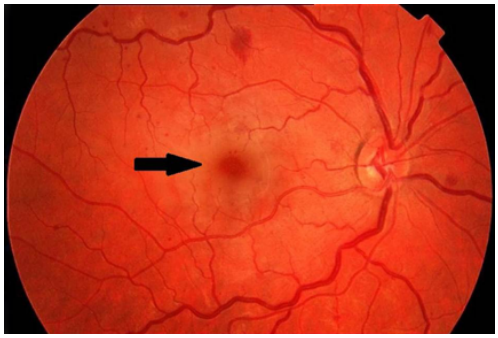
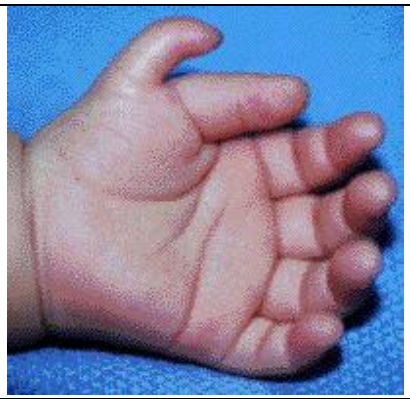
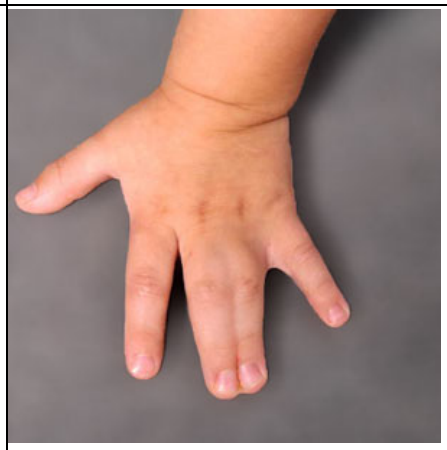
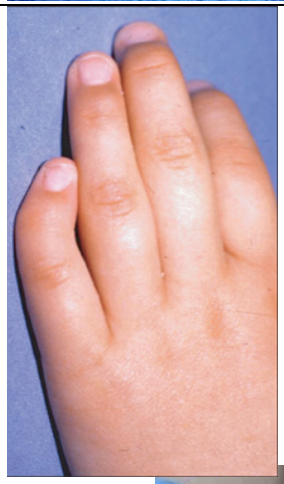
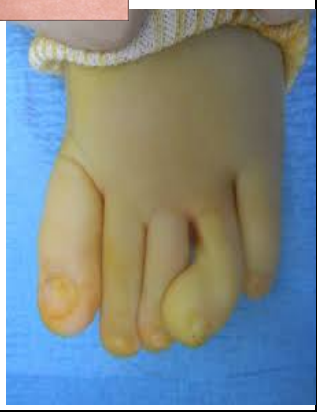
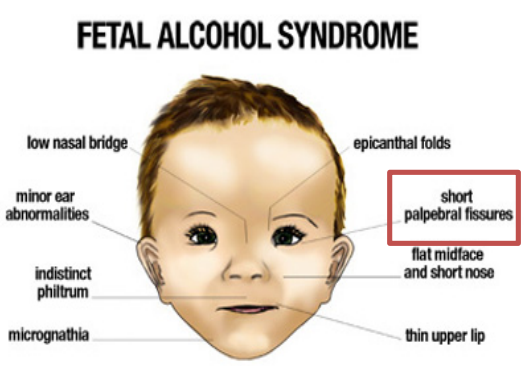
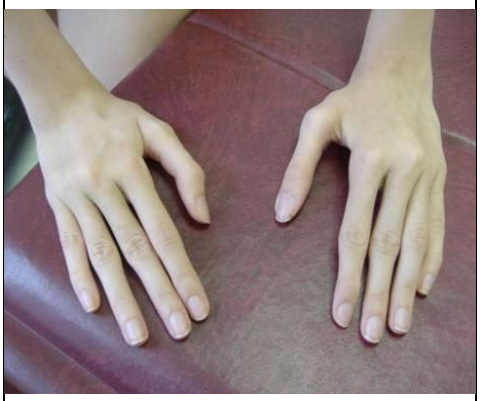
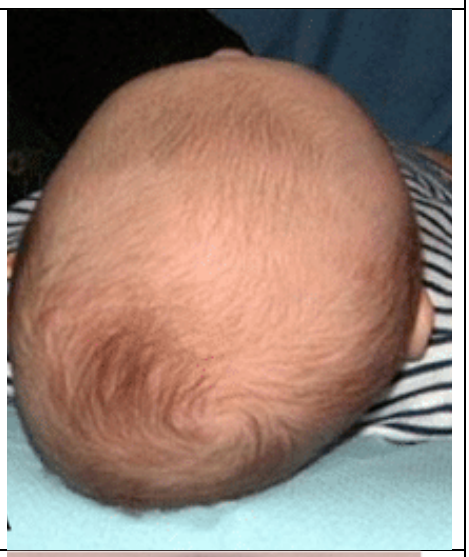
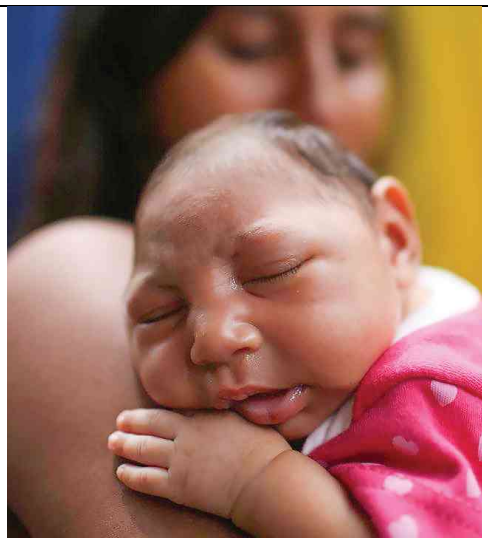
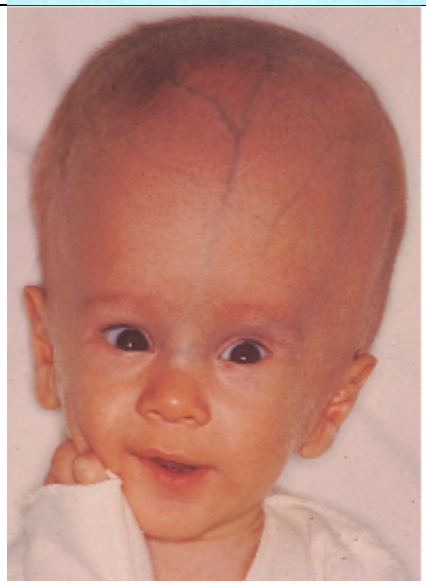
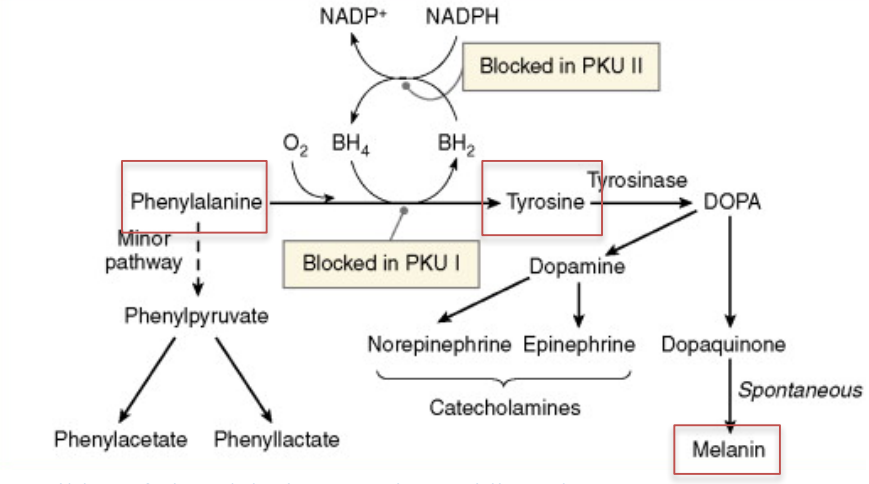
		
7,8,9	**10**	**11**
		

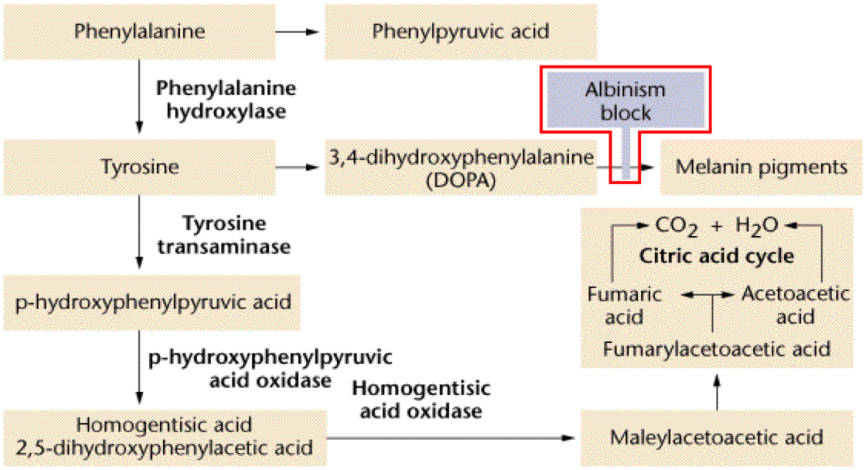
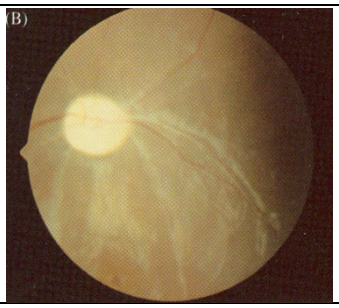
✻ Other Dysmorphologies:

Dysmorphology	Picture	Dysmorphology	Picture
Micrognathia aka receding chin		**Hypertolirism** (increased distance between the eyes)	
Cherry red spot Jewish lipid storage disease		**Polydactyly**	
Syndactyly	 	**Clinodactyly** curved medially	 

Dysmorphology	Picture	Dysmorphology	Picture
Microopthalmia with a short palpebral fissure (most characteristic), depressed nasal bridge, and mental retardation → Fetal alcohol syndrome		**Arachinodactyly** Seen in Marfan, hypermethionin-emia, or homocystinuria	
Congenital Cataract		**Plagiochepahly** (especially in prematurity) "راسه زي المعين"	
Microcephaly		**Macrocephaly** (because of hydrocephaly. Prominent veins indicating impeded venous return caused by high ICP)	

Examples of Metabolic Disorders

Disorder	Cause	Clinical Manifestations
Galactosemia (Autosomal Recessive)	Galactose-1-phosphate uridyl transferase deficiency	• Follows feeding with lactose containing (breast milk / formula) • Patient feeds poorly ,have vomiting, jaundice, hepatomegaly and hepatic failure • Chronic liver disease • Cataracts • Developmental delay develop if condition is untreated, if they were given galactose free diet you will avoid the social and mental damage but they might complain of dyslexia. • Treatment is **galactose-free milk/diet.**
Cystic Fibrosis Affects **EXOCRINE** mucus glands (Autosomal Recessive)	Loss of 3 DNA bases in a gene for the protein that transports chloride ions → salt balance upset	• A buildup of **thick** mucus in lungs and digestive organs. pancreas and liver • It is diagnosed by sweat test: measuring the chloride concentration in the sweat. +ve if > 60mEq, -ve if < 40 mEq • Detected in new born screening. • CFTR stands for cystic fibrosis transmembrane conductance regulator • CFTR is a cAMP dependent chloride channel found in the membrane of cells, responsible for the type of mucus produced.
Phenylketonuria (Autosomal Recessive)	Phenylalanine hydroxylase deficiency Thus cannot turn phenylalanine into tyrosine → buildup of phenylalanine in the body	 • Buildup of phenylalanine turns into acidic and ketotic molecules giving the patient the characteristic smell. In nurseries you might even detect the disease based on smell. • Phenyl pyruvic acid is what gives the urine its smell because its ketonic and acidic. • Loss of melanin → blue eyes are characteristic. Can be blonde. Note that melanin deficiency here doesn't reach the same levels as albinism. • Treatment is **phenylalanine-low milk/diet.**

Disorder	Cause	Clinical Manifestations
Albinism (Autosomal Recessive)	Genetic defect in an enzyme called **tyrosinase**. This enzyme helps the body to change the amino acid, tyrosine, into pigment.	 • Result is no melanin whatsoever. Melanin is concentrated in the iris, but these babies have ZERO melanin so their eyes are affected and you can see the **capillaries** through them hence the redness.
Congenital Adrenal Hyperplasia (CAH) (Autosomal Recessive)	Most common cause is 21-hydroxylase deficiency	• In addition to the enzyme deficiency, there are social and clinical problems associated with **ambiguous genitalia**. • Presentation: ○ Ambiguous genitalia should be found and treated early ○ Failure to Thrive ○ Dehydration ○ Salt-losing – hyponatremia ○ Hyperkalemia ○ Hypoglycemia ○ Hyperpigminatation ○ Maybe Shock
Homocystinuria (Autosomal Recessive) Note: Marfan is autosomal dominant!!	Cystathionine Synthase deficiency	• Resemble Marfan Syndrome "marfanoid habitus" + lens abnormalities. • Elevated homocystine levels affect collagen, result in a Marfanoid habitus, **downward** ectopia lentis (unlike Marfan with an upward lens dislocation), mental retardation and strokes, its harmful to the bones and body. Arachnodyctly.
Aminoacid disorders	-	• All present with lethargy, seizures, ketoacidosis, neutropenia, and hyperammonemia. Think of neonatal infxn 1st.
Glycogen storage diseases	-	Type I – Von Gierke Type II – Pompe Type III - Cori Type IV - Anderson Type V – Mcardle's Type VI - Her
Sphingolipidoses	-	 • E.g. Tay-Sachs disease in Jewish population. "cherry red spot" – not shown. • E.g. Gaucher's disease.: Gaucher cell in the bone marrow is diagnostic. Also **Organomegaly**. Skin & bones appearance. • Lipids can deposit in the **retina (pic to the left)**, in the thalamus etc.
Mucopoly-saccharidoses	-	• Hurler & Hunter's disease etc. • Remember corneal clouding is found only in HURLER.
Peroxisomal disorders	-	• Most famous is Zellweger Syndrome AKA Cerebro-hepato-renal syndrome.