SNS COLLEGE OF NURSING

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DEPARTMENT : Department of Nursing

COURSE NAME : B. Sc. (Nursing) II Year IV Semester

SUBJECT : Genetics

UNIT III : Genetic conditions of adolescents and adults

TOPIC : Inborn Errors of Metabolism

Inborn errors of metabolism

Inborn errors of metabolism
1. Introduction:

- **Inborn errors of metabolism** form a large class of genetic diseases involving congenital disorders of enzyme activities.
- The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products).
- In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or due to the effects of reduced ability to synthesize essential compounds.
- Inborn errors of metabolism are often referred to as **congenital metabolic diseases** or **inherited metabolic disorders**.
- Another term used to describe these disorders is "enzymopathies".

List of Inborn metabolic disorders

1. Disorders of carbohydrate metabolism - G6PD deficiency.
2. Disorders of amino acid metabolism- phenylketonuria, maple syrup urine disease.
3. Disorders of organic acid metabolism (organic acidurias) – Alkaptonuria.
4. Disorders of fatty acid oxidation and mitochondrial metabolism - Glutaric Acidemia.
5. Disorders of purine or pyrimidine metabolism - Lesch–Nyhan syndrome.
6. Disorders of steroid metabolism - congenital adrenal hyperplasia
7. Disorders of mitochondrial function - Kearns–Sayre syndrome
8. Disorders of Lysosomal storage disorder - Gaucher's disease

Disorders of carbohydrate metabolism - G6PD deficiency

Signs and symptoms

- Prolonged neonatal jaundice, possibly leading to kernicterus (arguably the most serious complication of G6PD deficiency)
- Hemolytic crises in response to:
- Illness (especially infections)
- Certain drugs (see below)
- Certain foods, most notably broad beans, from which the word favism derives
- Certain chemicals
- Diabetic ketoacidosis
- Hemoglobinuria (red or brown urine)
- Very severe crisis can cause acute kidney injury

Treatment

- Vaccination of

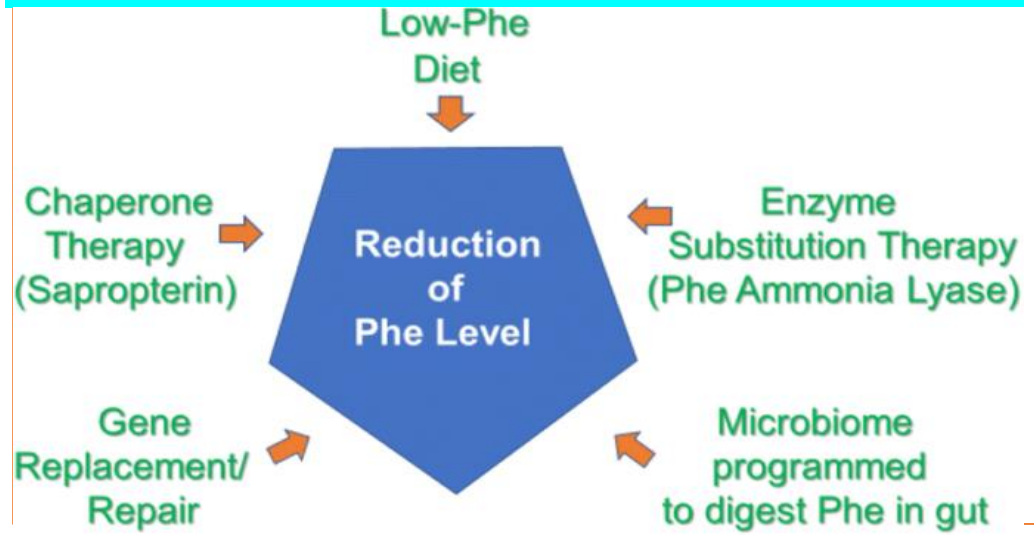
Hepatitis A and B

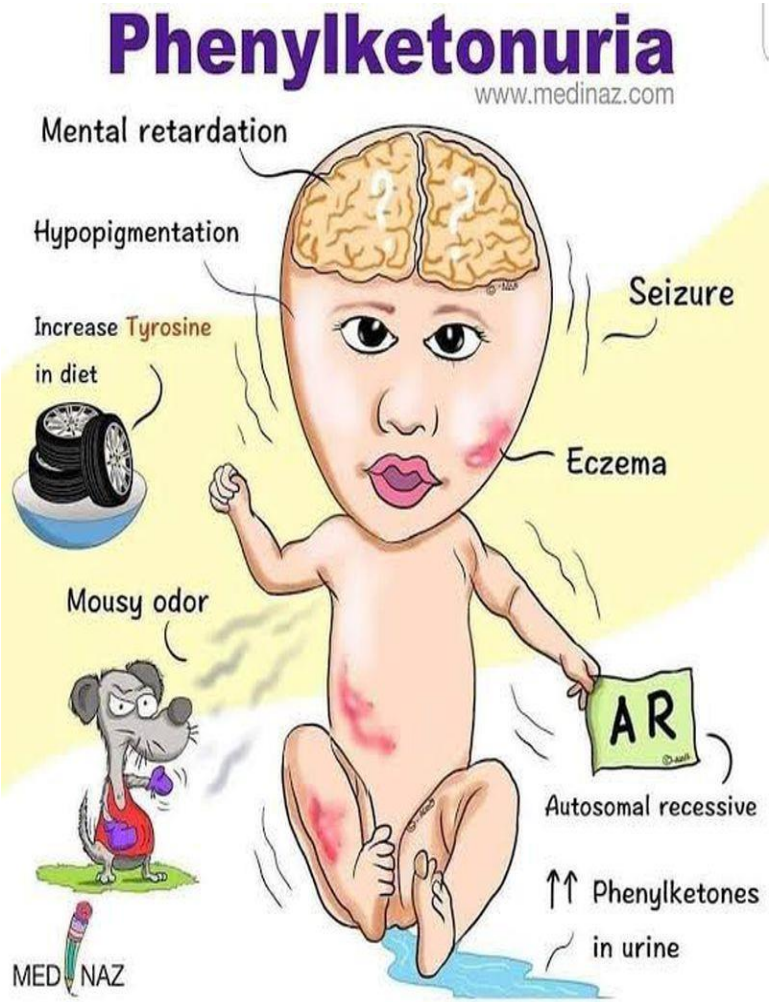
- Blood transfusion
- Haemodialysis- ARF
- Aspirin to be avoided
- Folic acid supplements to be given
- Vitamin –E and selenium(antioxidants)

Glucose-6-phosphate dehydrogenase is an enzyme which protects red blood cells, which carry oxygen from the lungs to tissues throughout the body. A defect of the enzyme results in the premature breakdown of red blood cells. This destruction of red blood cells is called hemolysis.

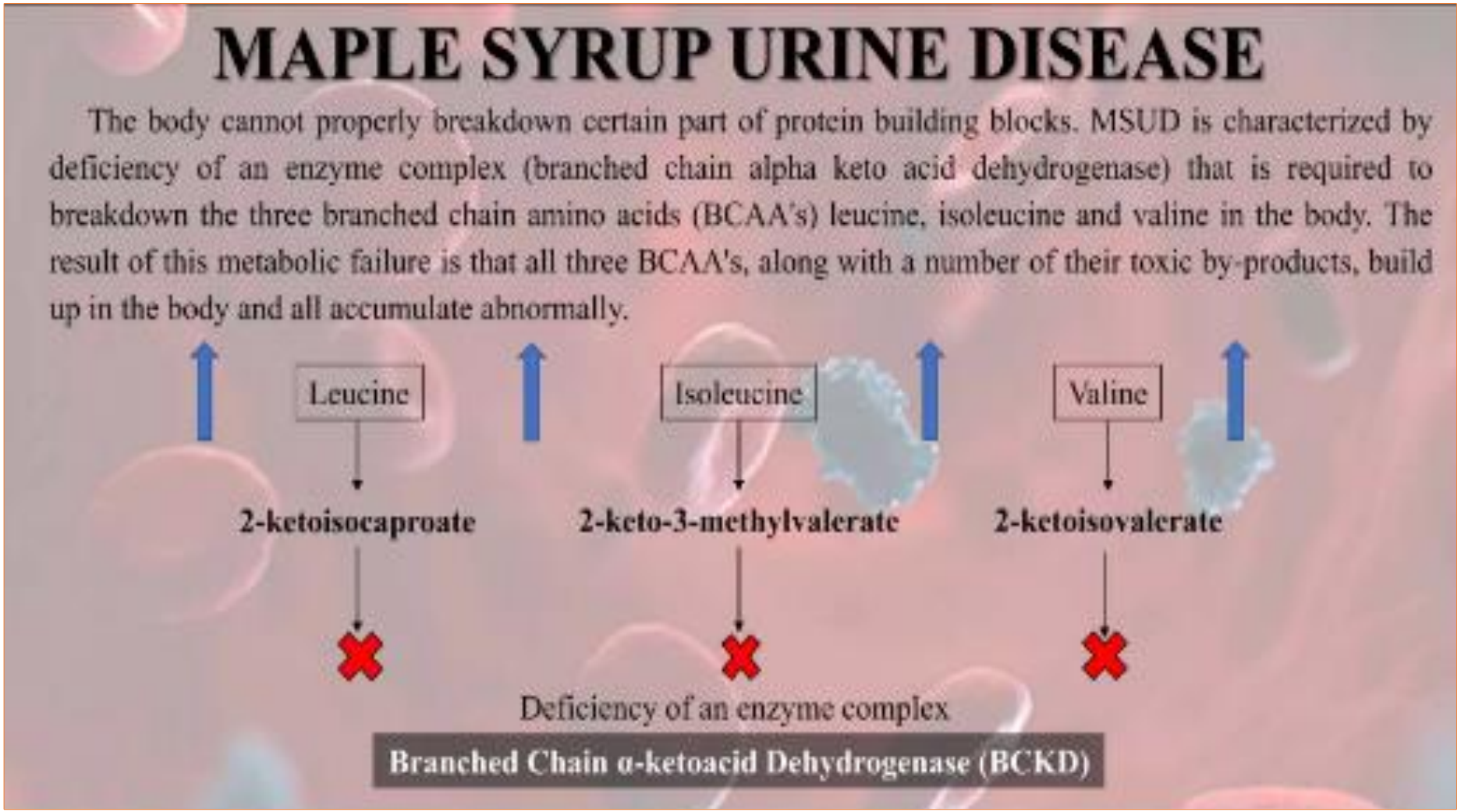
Disorders of amino acid metabolism- phenylketonuria, maple syrup urine disease

Phenylketonuria is an inherited genetic disorder. It is caused by mutations in the *PAH* gene, which can result in inefficient or nonfunctional phenylalanine hydroxylase, an enzyme responsible for the metabolism of excess phenylalanine. This results in the buildup of dietary phenylalanine to potentially toxic levels.





Maple syrup urine disease



Disorders of organic acid metabolism (organic acidurias) – Alkaptonuria

- Usually asymptomatic
- Infants shows darken diapers, (black nappies)
- Bluish pigmentation of sclera and ear.
- Pain in spine, hip and knee joints
- Osteoarthritis
- Heart valve damages
- Kidney stones formation.

An autosomal recessive condition

due to defect in the enzyme

(homogentisate1, 2-dioxygenase)

which precipitates in the degradation of tyrosine

as a result a toxic tyrosine byproduct

(HOMOGENTISIC ACID/ ALKAPTON)

accumulates in the blood and

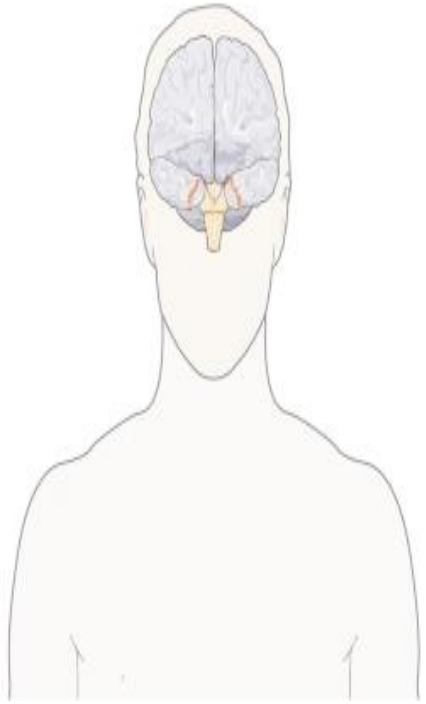
excreted in large amounts in urine

Treatment

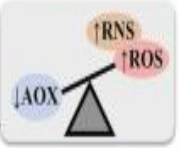
- The treatment of alkaptonuria is aimed at the specific symptoms.
- Activities that place significant physical stress to the spine and joints should be avoided.
- Patients receive anti-inflammatory medications or narcotics to treat joint pain.
- Physical and occupational therapy- to maintain the strength and flexibility of muscles and joints.
- Some individuals require surgical intervention.
- In older children and adults, high-doses of vitamin C is recommended because it hinders the accumulation and deposition of HGA and may slow down the progression of arthritis.
- Nitisinone (experimental drug), an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase, which mediates formation of HGA, has been reported.

Disorders of fatty acid oxidation and mitochondrial metabolism - Glutaric Acidemia

Pathomechanisms of brain damage in Glutaric Acidemia type 1

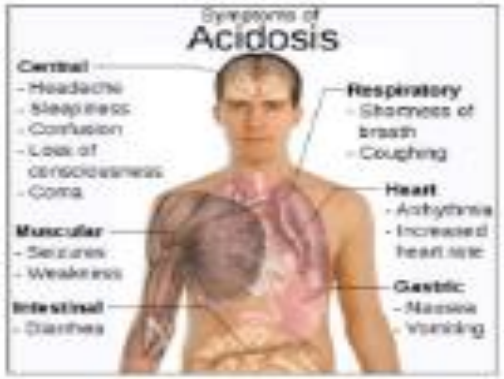


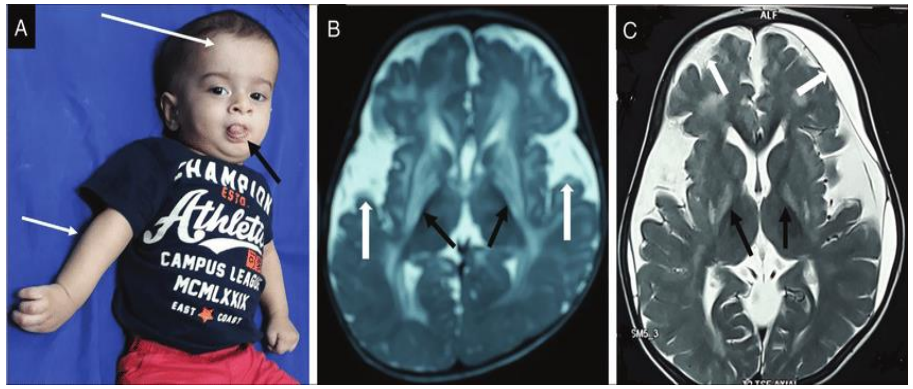
- Glutamatergic and GABAergic disturbance
- Oxidative stress



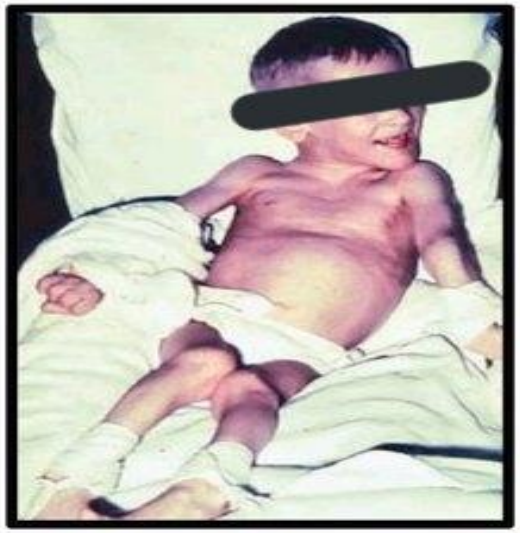
- Bioenergetics disruption
- Microglial activation and neuroinflammation
- Reactive astrogliosis with neurotoxic factors release
- Myelination disturbance and oligodendrocyte dysfunction
- Vascular and blood-brain barrier alterations

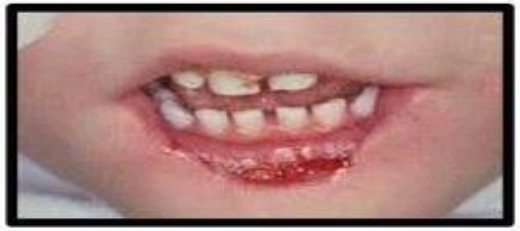
- **Metabolic crisis:**
  - Weakness / irritability
  - Nausea / diarrhea / vomiting
  - Hypoglycemia
  - Acidosis
  - Stop breathing
  - Seizures
  - Coma
- **Complications:**
  - Organ damage
  - Learning disabilities





Disorders of Purine metabolism





Lesch Nyhan Syndrome

❖ Clinical features

- ✓ Self-injury (Most distinctive behavioral problem)
  - ▪ Fingers & mouth biting
  - ▪ Head banging
- ✓ Dystonia
- ✓ Chorea
- ✓ Hypotonia
- ✓ Ballismus
- ✓ Developmental delay

❖ Mode of inheritance?

- ✓ X-linked recessive
- ✓ HPRT1 gene
- ✓ Defect in purine metabolism

❖ Laboratory finding ?

- ✓ Hyperuricemia

❖ Complications :

- ✓ Gouty arthritis
- ✓ Kidney & bladder stones
- ✓ Renal failure

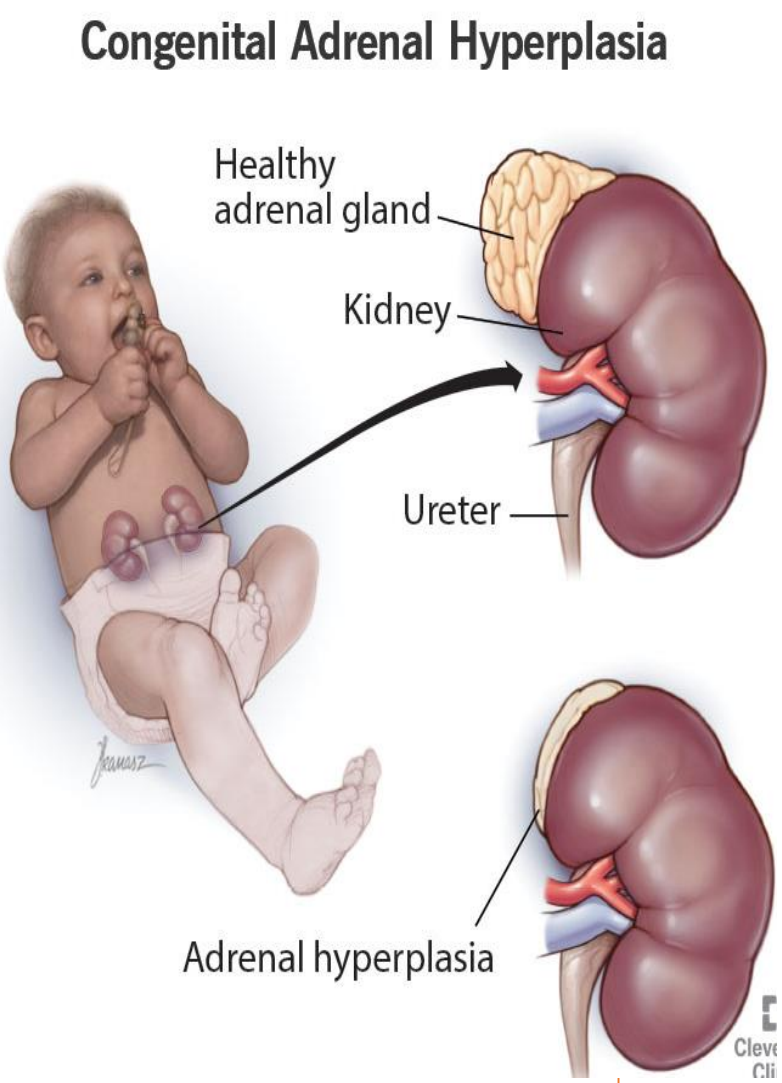
❖ Most common cause of death?

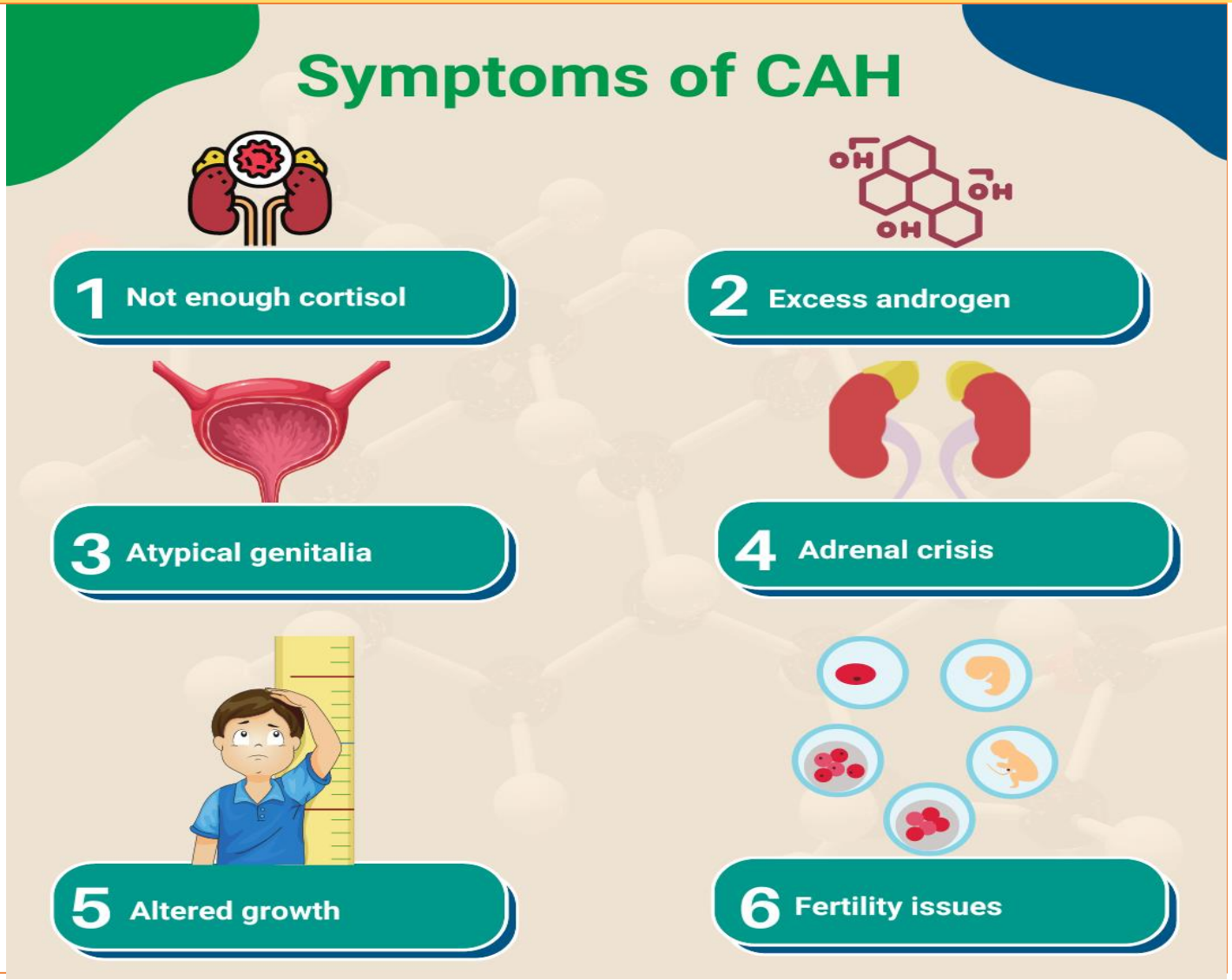
- ✓ Renal failure

❖ Treatment :

- ✓ Allopurinol
- ✓ High fluid intake
- ✓ Behavioral therapy

Disorders of steroid metabolism – congenital adrenal hyperplasia



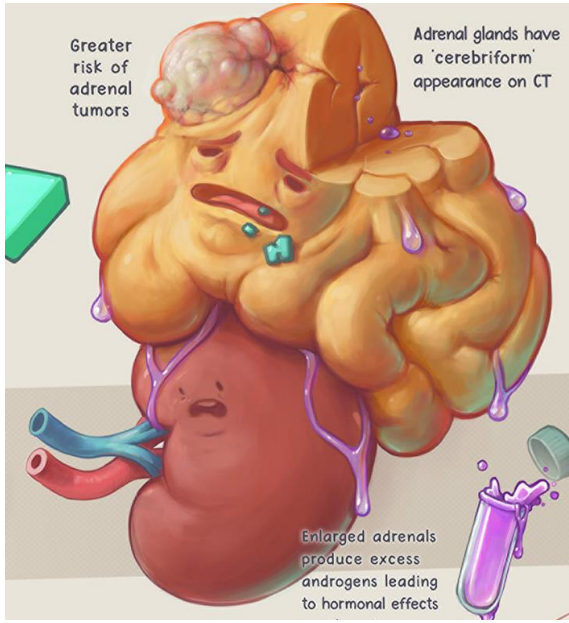


Disorders of steroid metabolism – congenital adrenal hyperplasia

- ✓Hydrocortisone should be administered in physiological doses of 10-15mg/m2/day during infancy.
- ✓Hydrocortisone should be supplemented in thrice daily schedule. The morning dose should be given as early as possible in the morning.
- ✓Stress doses of steroids to be continued during illness and stressful situations in all patients of CAH
- ✓Fludrocortisone should be supplemented in all infants with classical CAH irrespective of genotype/ phenotype. All infants with salt losing should be prescribed oral salt supplements 1-3 g day.

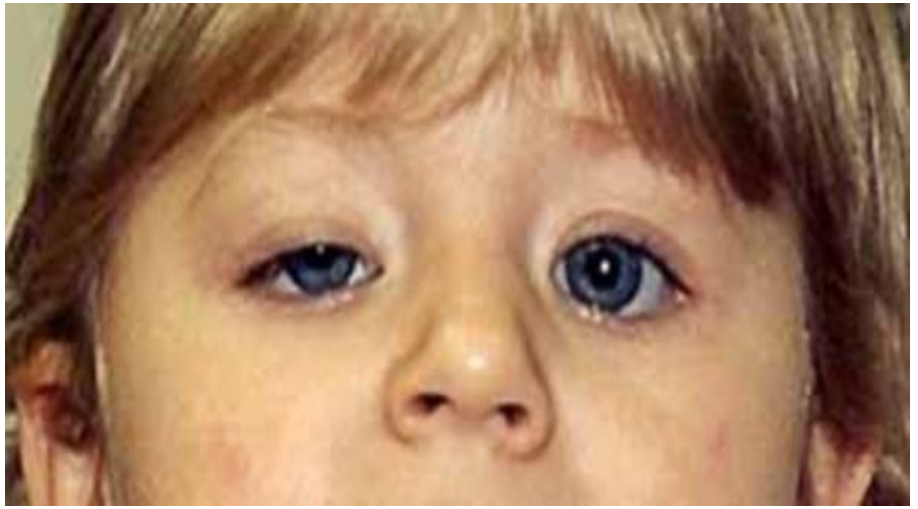
Disorders of steroid metabolism – congenital adrenal hyperplasia

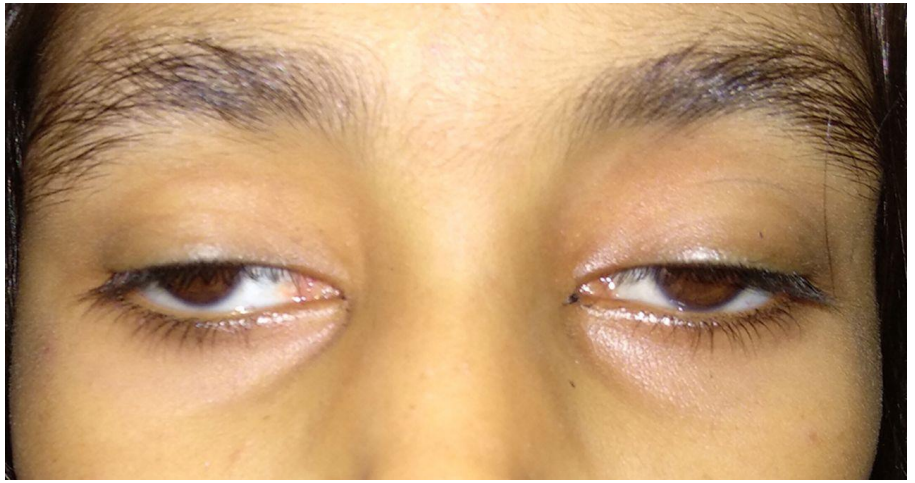
- ✓ Maintain airway, breathing and circulation.
- ✓ Restore intravenous hydration by intravenous route using a wide bore needle.Infuse isotonic saline at 20 mL/ kg over 10 minutes if signs of shock are present (maximum upto 60 mL/kg).
- ✓ Further fluid replacement to be guided by clinical signs of shock or over-hydration. Newborns should be continued on 1.5-2 times fluid as maintenance therapy (half normal saline in 5% dextrose solution).
- ✓ Check and correct hypoglycaemia. Administer 5 mL/kg of 10% dextrose if low blood sugar is detected.
- ✓ Administer Intravenous hydrocortisone at 50-100 mg/m2 bolus followed by 50-100 mg/m2 /d in four divided doses (6 hourly). Usual dose in newborn babies is approximately 25 mg bolus followedby 5-6 mg every 6 hourly.
- ✓ Continue intravenous route till patient is fit to consume orally.
- ✓ Check and correct any dyselectrolytemia.
- ✓ Monitor vitals, intake, output and sensorium.
- ✓ Mineralocorticoid replacement may be resumed when patient is stable and shifted to oral hydrocortisone maintenance doses.



Disorders of mitochondrial function - Kearns–Sayre syndrome

KSS is characterized by the onset of ophthalmoparesis and pigmentary retinopathy before age 20 years. Other frequently associated clinical features include cerebellar ataxia, cardiac conduction block, raised cerebrospinal fluid (CSF) protein content, and proximal myopathy.





KSS

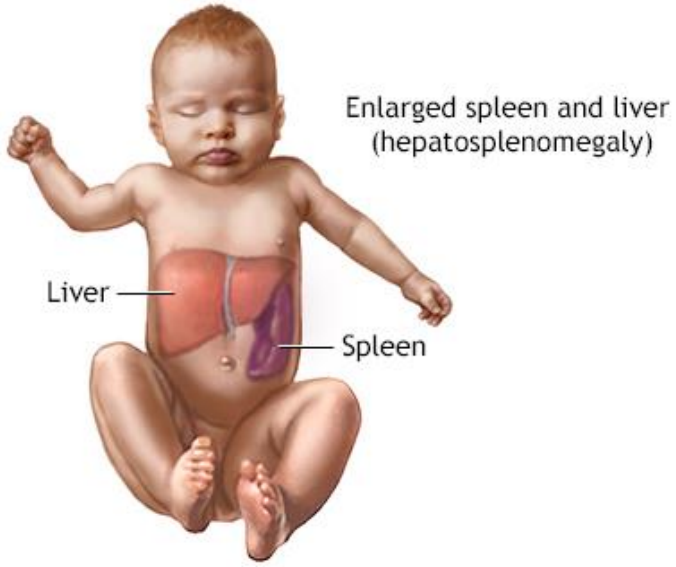
- KSS is caused 5000 base deletion in mitochondrial DNA.
- > 1 genome can be in a cell at any given time.

Treatment:

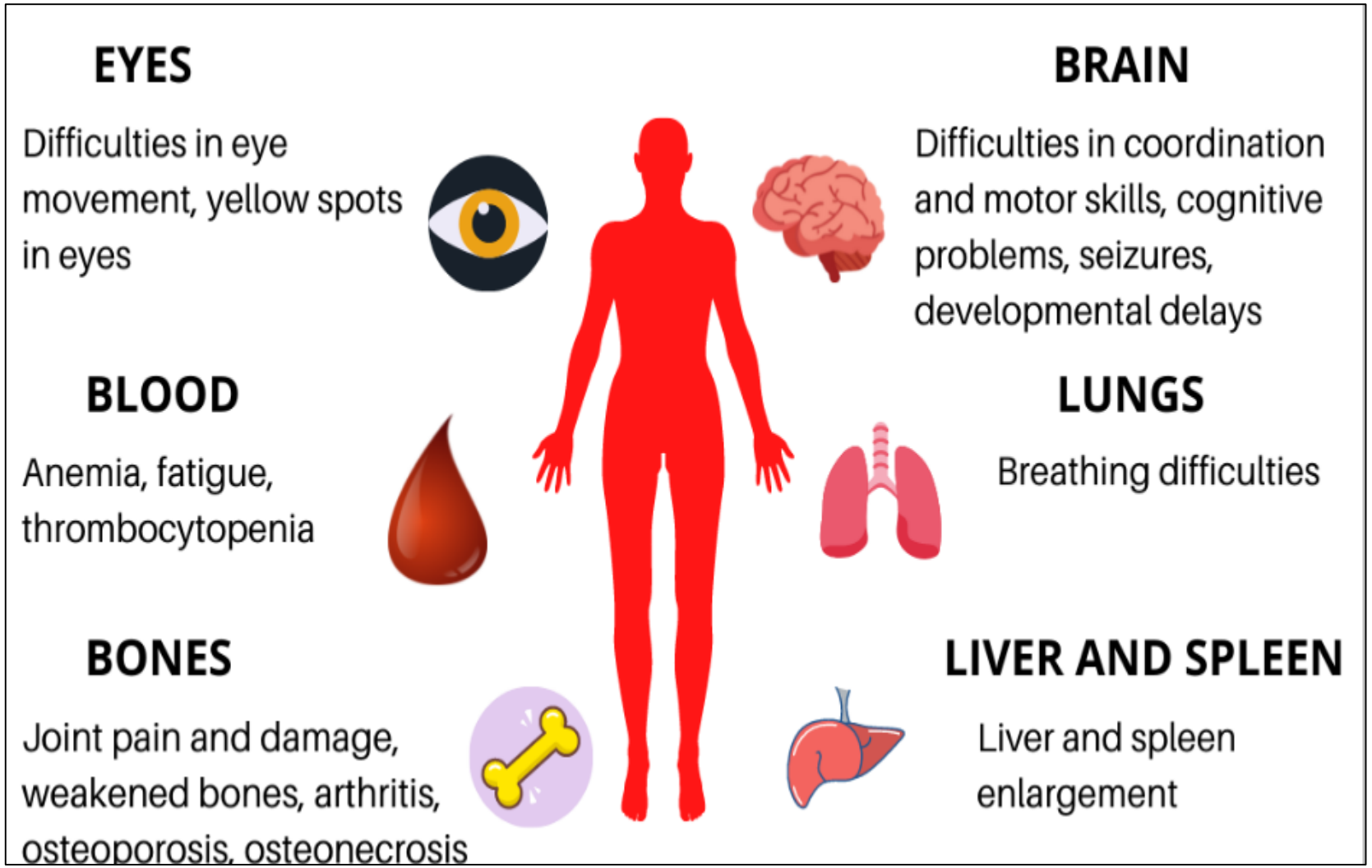
1. Coenzyme Q10 (CoQ10) administration and vitamin supplements.
2. Insulin for DM.
3. Pace maker for AV block
4. Surgery to correct visual problems

Disorders of Lysosomal storage disorder - Gaucher's disease

- Gaucher disease is a lysosomal storage disorder (LSD) that causes fatty substances to build up in the body's organs and bone marrow.
- Gaucher disease is caused by mutations in the GBA gene, which breaks down the enzyme glucocerebrosidase (GCase).
- Without enough GCase, fat builds up in macrophages, which are immune cells that accumulate in the liver, spleen, and bone marrow



Disorders of Lysosomal storage disorder - Gaucher's disease **SIGNS AND SYMPTOMS**



Disorders of Lysosomal storage disorder - Gaucher's disease

Treatment:

- No permanent cure for Gaucher disease, however various treatment options available to control symptoms.
- Enzyme replacement therapy – replaces the deficiency of the glucose cerebrosidase enzyme with artificial enzymes. It involves intravenous infusions every 2 weeks.
- Substrate reduction therapy – reduce the glucocerebroside level in the body.
- Osteoporosis drugs – taken for strengthening and rebuilding bones.
- Miglustat and Eliglustat – interfere with the production of fatty chemicals and inhibit more production of them.
- Removal of spleen before enzyme replacement therapy is performed at times. Bone marrow transplant is another surgical procedure performed as a treatment for Gaucher disease.

Summary

Inborn errors of metabolism comprise a large class of genetic diseases involving disorders of metabolism.

The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products).

In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds.

Conclusion

- Thus inborn errors comprises a large class of genetic diseases involving the disorders of metabolism.

Assessment

- Define Inborn errors of Metabolism.
- List out any 4 types of Inborn errors of metabolism.
- Enumerate the causes for metabolic genetic disorders .
- Explain the signs and symptoms of Gaucher’s disease
- Expand KSS.

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Thank you !