Inborn Errors Of Tyrosine Metabolism
• Tyrosine is non-essential amino acid, and it derives from two sources, diet and hydroxylation of phenylalanine
• Tyrosine is both glucogenic and ketogenic, its catabolism proceeds predominantly in the liver cytosol, results in the formation of fumarate and acetoacetate.
• The first step of tyrosine catabolism is conversion into 4-hydroxyphenyl-pyruvate by cytosolic tyrosine aminotransferase.
• **Transamination** of tyrosine can also be accomplished in the liver and in other tissues by *mitochondrial aspartate aminotransferase*, but this enzyme plays only a minor role under normal conditions. Its role increased when tyrosine levels increased in cytosol.
• The intermediates of tyrosine catabolism, maleylacetoacetate and fumarylacetoacetate, can be reduced to succinylacetoacetate, followed by decarboxylation to succinylacetone.
• **Succinylacetone** is the most potent known inhibitor of the heme biosynthetic enzyme, *5-aminolevulinic acid dehydratase* (porphobilinogen synthase).
The tyrosine catabolic pathway.

1. Tyrosine aminotransferase (deficient in tyrosinaemia type II);
2. 4-hydroxyphenylpyruvate dioxygenase (deficient in tyrosinaemia type III, hawkinsinuria, site of inhibition by NTBC);
3. Homogentisate dioxygenase (deficient in alkaptonuria);
4. Fumarylacetoacetase (deficient in tyrosinaemia type I);
5. Aspartate aminotransferase;
6. 5-aminolevulinic acid (5-ALA) dehydratase (porphobilinogen synthase). Enzyme defects are depicted by solid bars across the arrows.
Five inherited disorders of tyrosine metabolism are known:

- **Hereditary tyrosinaemia type I** is characterised by progressive liver disease and renal tubular dysfunction with rickets.
- **Hereditary tyrosinaemia type II** (Richner-Hanhart syndrome) presents with keratitis and blisterous lesions of the palms and soles.
- **Tyrosinaemia type III** may be asymptomatic or associated with mental retardation.
- **Hawkinsinuria** may be asymptomatic or presents with failure to thrive and metabolic acidosis in infancy.
- **Alkaptonuria** symptoms of osteoarthritis usually appear in adulthood.
Hereditary Tyrosinaemia Type I
Tyrosenemia Type I
(Hepatorenal Tyrosinaemia)

- It is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase, which is mainly expressed in the liver and kidney.
- **It is an autosomal recessive disorder**
- The FAH gene has been localised to 15q 23–25 and more than 40 mutations have been reported.
- It affects approximately one in 100,000 to 120,000 births.

(Because of the inconsistent and confusing nature of its clinical presentation, it is estimated that fewer than 50% of affected individuals are diagnosed while alive. In the general US population, the carrier frequency is estimated at 1:150 to 1:100.)
Tyrosenemia Type I
(Hepatorenal Tyrosinaemia)

Clinical Presentation

• The clinical manifestations of tyrosinaemia type I are very variable.
• Clinically, it can be classified based on the age at onset of symptoms into:
  - 1- **Acute form** that manifests before 6 months of age with acute liver failure.
  - 2- **Subacute form** presenting between 6 months and 1 year of age with liver disease, failure to thrive, coagulopathy, hepatosplenomegaly, rickets and hypotonia.
  - 3- **Chronic form** that presents after the first year with chronic liver disease, renal disease, rickets, cardiomyopathy and/or a porphyria-like syndrome.
General Symptoms

• reduced weight gain and growth rate
• diarrhea and vomiting
• Jaundice
• **smells like cabbage**
• increased nosebleeds
• acute neurological crises, Complications include seizures, self-mutilation, respiratory paralysis and death.
• liver cirrhosis or hepatocellular carcinoma
• liver and kidney failure
• Mortality is high in untreated patients
Renal tubular involvement

- In the more chronic form of the untreated disorder (symptoms develop after age six months) renal tubular involvement is the major manifestation.
- The renal tubular dysfunction involves a Fanconi-like renal syndrome with **generalized aminoaciduria, phosphate loss**, and, for many, renal tubular acidosis.
- The continued renal loss of phosphate is causing **rickets**; serum calcium concentrations are usually normal.
Neurologic crises

- Untreated children may have repeated neurologic crises similar to those seen in older individuals with acute intermittent porphyria.
  - These crises include change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure requiring mechanical ventilation.
  - Crises can last one to seven days.
  - It was reported that 42% of untreated French Canadian children with tyrosinemia type I had experienced such episodes.
  - In an international survey, it was reported that 10% of deaths in untreated children occurred during a neurologic crisis.
Metabolic Derangement

- Deficiency of the enzyme fumarylacetoacetate hydrolase causes accumulation of maleylacetoacetat (MAA) and fumarylacetoacetate (FAA), and their derivatives, succinylacetone (SA) and succinylacetoacetate (SAA).

- The effects of FAA and MAA occur only in the cells of the organs in which they are produced; liver and kidney, and cause hepatorenal damage. These compounds are not found in body fluids of patients.

- FAA accumulate in hepatocytes, causing cellular damage and apoptosis.

- On the other hand, their derivatives, SA and SAA are detectable in plasma and urine.
Metabolic Derangement

- Succinylacetone is a potent inhibitor of the enzyme 5-ALA dehydratase. 5-ALA, a neurotoxic compound, accumulates and is excreted at high levels in patients with tyrosinemia type I may cause the acute neurological symptoms.
- SA is also known to disrupt renal tubular function, heme synthesis and immune function
Biochemical finding:

- Elevated plasma concentration of tyrosine, methionine, and phenylalanine.
- Elevated urinary concentration of tyrosine metabolites $p$-hydroxyphenylpyruvate, $p$-hydroxyphenyllactate, and $p$-hydroxyphenylacetate.
- Increased succinylacetone concentration in the blood and excretion in the urine.
- Increased urinary excretion of the compound $\delta$-ALA secondary to inhibition of the enzyme $\delta$-ALA dehydratase by succinylacetone in liver and circulating red blood cells.
Diagnosis

1- Elevated plasma levels of tyrosine, phenylalanine and methionine.
2- Biochemical tests of liver function are abnormal.
3- A Fanconi-type tubulopathy is often present with aminoaciduria, phosphaturia and glycosuria (because of renal affection).
4- Elevated levels of succinylacetone in dried blood spots. **Succinylacetone is the hallmark of the diagnosis.**
5- Reduced erythrocyte 5-aminolevulinate dehydratase activity and increased urinary 5-ALA excretion.
6- Confirmation of the diagnosis requires enzyme assay in liver biopsy, fibroblasts, lymphocytes or dried blood spots. DNA testing for mutation detection.
Newborn Screening

- **Succinylacetone**, measured directly from the newborn blood spot by tandem mass spectroscopy.
- **Delta-ALA-dehydratase (PBG synthase) enzyme activity**, measured in the newborn screening program in Quebec, Canada. Succinylacetone is then measured in the urine of infants with apparent δ-ALA dehydratase deficiency.

Prenatal Diagnosis

If the causative mutations in a pregnancy at risk are known, antenatal diagnosis is best performed by mutation analysis on chorionic villus sampling (CVS) or amniocytes. Alternative methods include FAH assay on CVS or amniocytes determination of SA levels in amniotic fluid. Assay for elevated SA levels in amniotic fluid is very reliable and can be performed as early as 12 weeks.
Treatment

1--Nitisinone (Orfadin®). (NTBC) was approved by the Food and Drug Administration for treatment of tyrosinemia type I. Nitisinone blocks parahydroxyphenylpyruvic acid dioxygenase (p-HPPD), the second step in the tyrosine degradation pathway, and prevents the accumulation of FAA and its conversion to succinylacetone. Nitisinone should be prescribed as soon as the diagnosis of tyrosinemia type I is confirmed.

2– Tyrosine and phenylalanine restricted diet.

3– Liver transplantation.
Tyrosinemia Type I

Phenylalanine → Tyrosine

Tyrosine → 4-OH-phenylpyruvate

Homogentisate → Maleyl-acetoacetate

Fumaryl-acetoacetate → Fumarate + Acetoacetate

Succinylacetone

5-Aminolevulinate → Porphobilinogen → Heme Synthesis

Porphobilinogen

2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC; Nitisinone; Orfadin)
Hereditary Tyrosinaemia Type II

Ocluocutaneos Tyrosinemia
Clinical Presentation

- **Ocular lesions** (about 75% of the cases), **skin lesions** (80%), and **neurological complications** (60%), or any combination of these.
- The disorder usually presents in infancy but may become manifest at any age.
- Eye symptoms are often the presenting problem and may start in the first months of life with photophobia, lacrimation and intense burning pain. If untreated, serious damage may occur with corneal scarring, visual impairment and glaucoma.
- Skin lesions commonly occur on the palms and soles. They begin as blisters or erosions with crusts and progress to painful hyperkeratotic plaques.
Clinical Presentation cont..

- The neurological complications are highly variable, some patients are developmentally normal whilst others have variable degrees of developmental retardation. More severe neurological problems, including microcephaly, seizures, self-mutilation and behavioural difficulties.
Keratosis Palmoplantaris

(*hyperkeratosis*)
Metabolic Derangement

- Tyrosinaemia type II is due to a defect of hepatic cytosolic tyrosine aminotransferase.
- As a result of the metabolic block, tyrosine concentrations in serum and cerebrospinal fluid are markedly elevated.
- The accompanying increased production of the phenolic acids 4-hydroxyphenyl-pyruvate, -lactate and -acetate is a consequence of tyrosine catabolism by mitochondrial aminotransferase.
- Corneal damage is related to crystallization of tyrosine in the corneal epithelial cells.
- Skin lesions may result from excessive intracellular tyrosine.
- The etiology of the neurological manifestations is unknown, but it is believed that hypertyrosinaemia is involved.
Genetics

- Tyrosinaemia type II is inherited as an autosomal recessive trait.
- The gene is located at 16q22.1-q22.3.
- Twelve different mutations have so far been reported in the tyrosine aminotransferase gene.
- Prenatal diagnosis has not been reported.
Diagnosis

1- Increased plasma tyrosine concentrations (above 1200 μmol/L)

2-Urinary excretion of the phenolic acids 4-hydroxyphenylpyruvate, -lactate, -acetate is highly elevated and N-acetyltyrosine and 4-tyramine. These give positive nitrosonaphthol test.

3-The diagnosis can be confirmed by enzyme assay on liver biopsy.

4-mutation analysis.
Treatment

- Phenylalanine and tyrosine-restricted diet to maintain plasma tyrosine levels of 200–400 μmol/l using a combination of a protein-restricted diet and a phenylalanine and tyrosine free amino acid mixture.
- The skin and eye symptoms resolve within weeks.
Hereditary Tyrosinaemia Type III
Clinical Presentation

- Rare disorder.
- The full clinical spectrum of this disorder is unknown.
- Many of the patients have presented with neurological symptoms including intellectual impairment, ataxia, increased tendon reflexes, tremors, microcephaly and seizures.
- Some patients have been detected by the finding of a high tyrosine concentration on neonatal screening.
- The most common long-term complication, intellectual impairment, found in 75% of the reported cases.
Metabolic Derangement

- Tyrosinaemia type III is due to deficiency of 4-hydroxyphenylpyruvate dioxygenase (HPD) which is expressed in liver and kidney.
- As a result of the enzyme block there is an increased plasma tyrosine concentration and increased excretion in urine of 4-hydroxyphenylpyruvate and its derivatives 4-hydroxyphenyllactate and 4-hydroxyphenylacetate.
- The aetiology of the neurological symptoms is not known, but they may be related to hyper tyrosinaemia as in tyrosinaemia types I and II.

Genetics

- It is an autosomal recessive disease.
- The HPD gene locus on chr 12q24-qter and 5 mutations associated with tyrosinaemia III have been described.
Diagnosis

- Elevated plasma tyrosine levels of 300–1300 µmol/l.
- Elevated urinary excretion of 4-hydroxyphenylpyruvate, -lactate and -acetate.
- Diagnosis can be confirmed by enzyme assay in liver or kidney biopsy specimens.
- Mutation analysis.

Treatment

- low-phenylalanine and tyrosine diet to maintain plasma tyrosine levels between 200 and 400 µmol/l.
Alkaptonuria
Alkaptonuria

- Alkaptonuria was first described in the 16th century.
- Characterized in 1859, it provided the basis for Garrod’s classic ideas concerning heritable metabolic disorders.
- It is autosomal recessive disorder, rare disorder.
- Enzyme deficiency: homogentisate oxidase in liver and kidneys
- The metabolic defect causes a characteristic excretion of large amounts of homogentisic acid in urine.
- No elevation of homogentisic acid in blood.
- This disorder is a model for the no-threshold metabolic disorder in which the metabolic intermediates is detected only in urine.
- No symptoms in infants and childhood. Young children shown skin discoloration.
- Deposition of polymerized homogentisic acid in connective tissues leads to degenerative joint disease in adult life.
Alkaptonuria

- There is arthritis and connective tissue pigmentation (ochronosis) due to oxidation of homogentisate to benzoquinone acetate, which polymerizes and binds to connective tissue. – dark pigment is also deposit in certain tissue, such as the ear wax, cartilage and joints, and affected adults are prone to develop arthritis in large joints.
- The urine turns black on exposure to air or addition of alkali, due to oxidation of excreted homogentisate (black pigment).
- Diagnosis can be confirmed by detection of homogentisic acid in urine, qualitative and quantitative.
- The molecular basis of alkaptonuria has been demonstrated to be defects in the gene coding for homogentisic acid oxidase (symbol HGO). The HGO gene is mapped to chromosome 3q21-q23; 14 exons over 60 kb of genomic DNA.
- No treatment is needed, but diet low in phenylalanine and tyrosine may prevent joint damage later on.
The bilateral deposition of ochronotic pigment in the scleras, best seen in the left eye.
BLACK URINE

BLACK CARTILAGE

BLACK NAILS (OCHRONOSIS), SKIN
Dark pigment is deposit in certain tissue,