Welcome students to a very interesting session of Z0C106 Biochemistry and Metabolic

Processes.

We are going to have a look at Unit 5 Amino Acid Metabolism under that the subtopic

“Inborn errors of amino acid catabolism: Alkaptonuria” is the topic of discussion today.

I'm Dr. Deeparani Prabhu, Assistant Professor from PESRSN College of Arts and

Science, Farmagudi, Ponda, Goa.

This module will outline the Inborn Errors of Amino Acid Catabolism.
Introduction to Alkaptonuria. Biochemical pathway of Alkaptonuria, Clinical symptoms of Alkaptonuria. Diagnosis and treatment of Alkaptonuria.

At the end of the session, a student will be able to understand the Inborn errors of amino acid catabolism. Also will be able to explain Alkaptonuria. Elaborate about the biochemical pathway of Alkaptonuria. Will be able to study the clinical symptoms of Alkaptonuria. Will be able to tell about the diagnosis and treatment of Alkaptonuria.

Inborn Errors of Amino Acid Catabolism: Alkaptonuria.

Before we go on to what exactly is Alkaptonuria let us first see, what an amino acid is.
Amino acid is an organic molecule comprising of a carboxylic acid group and an amino group that are each attached to a carbon atom called the alpha carbon.
A specific side chain known as R group is also attached to the alpha carbon.
Amino acids are building blocks of proteins. 20 different amino acids make up the proteins in mammals and humans. Proteins work as structural proteins and also as enzymes. They can also be metabolized to yield energy.
Essential amino acids are provided to the body through diet, whereas non essential amino acids are synthesized by the body.
Phenylalanine is an essential amino acid where as tyrosine is non essential amino acid. Most of the non essential amino acids are synthesized from glucose. Tyrosine is synthesized from the metabolism of phenylalanine.

Inborn errors of metabolism or IEM's are a large group of rare genetic diseases caused by a defect in an enzyme or transport protein, which results in a block in a metabolic pathway.

Toxic accumulations of the substrates, before the block, intermediates from the alternative metabolic pathway, defects in energy production or a combination of all these metabolic changes caused the clinical manifestation of these diseases.

IEM’s are caused by mutations in genes coding for proteins that function in metabolism.

The disorders are inherited as Autosomal Recessive, whereas Autosomal dominant and X linked disorders are also present.

AKU or Alkaptonuria was the first human disorder that was recognized by Sir Archibald Garrod over 100 years ago to conform to the principles of Mendelian autosomal recessive inheritance. In 1998 in his Croonian lecture, he introduced the concept of Inborn errors of metabolism to describe AKU and three other inherited disorders, albinism, cystinuria and pentosuria.

After 50 years Bert la du and colleagues identified the enzymatic defect as deficiency of Homogentisate 1, 2-dioxygenase, an enzyme in the metabolism of tyrosine and phenylalanine.

AKU, occurs worldwide with the highest frequencies reported in Slovakia and the Dominican Republic.In the United States, Alkaptonuria has a prevalence of 1 case per 2, 50,000 to 1 million live births.

Alkaptonuria is a rare metabolic disease caused by deficiency in Homogentisic acid oxidase leading to accumulation of Homogentisic acid.

Let us have a look at the biochemical pathway, which shows the usual amino acid metabolism of phenylalanine and tyrosine and the corresponding deficient or absent enzymes in the metabolic disorders of phenylalanine and tyrosine.

Here I'll be discussing only that part which is related to Alkaptonuria.

If we look at the first compound Phenylalanine, which is our first substrate.

It is metabolised to form Tyrosine and this reaction is catalyzed by the enzyme Phenylalanine hydroxylase.

The Tyrosine is further catabolized to form para Hydroxyphenyl pyruvate.

P- hydroxyphenyl pyruvate is further catabolized to form Homogentisate. This reaction is also being catalyzed by an enzyme which is called para hydroxyphenyl pyruvate dioxygenase.

The fate of Homogentisate will be its conversion to 4-Maleyl acetoacetate by the enzyme, in the presence of the enzyme Homogentisate oxidase.

Now in case of the patients who are suffering from Alkaptonuria, they are deficit in this particular enzyme.

As a result, Homogentisate gets accumulated. The Homogentisate which gets accumulated, it is further oxidized by Polyphenol oxidase to Benzoquinone acetate which undergoes polymerization to produce a pigment called ‘Alkapton.’

Alkapton binds to tissues of connective tissue, bones and various organs, resulting in a condition known as “Ochronosis.” The pigment appears brown or ochre hence the name.

This is a classical picture of a patient suffering from Alkaptonuria. You can see the pigmentation around the lip region of the patient where you can see the brown spots.

Now in case of the ochronosis diagnosis, in the infants, the dark staining of the diapers can indicate the disease. In the infants, but usually no symptoms are present until later stage of life.

So change in color of the urine on standing to brown or dark black. That is, coke color is observed in patients of Alkaptonuria.

If we have a look at the symptoms of Alkaptonuria, the illness is characterized by Homogentisic acid urea.

That is, the patients urine contains elevated levels of Homogentisic acid which is oxidized to a dark pigment on standing.

Black ochronotic pigmentation of cartilage and collagenous tissue.

In the longer term, arthritis and premature degeneration of joints occurs in many patients. The spine is initially involved, followed by the knees, shoulders and hips.

Small peripheral joints are usually spared. In the radiographs multiple vacuum discs, disc space,ossification and osteoarthritic changes in the spine are seen.

Bluish brown discoloration of ear pinna, sclera and nasal cartilage is also seen.

Diagnosis:

Change in color of the urine on standing to brown or dark color is the most important feature.

Urine gives positive test with ammonical silver nitrate due to strong reducing activity of homogentisate.

Urine becomes black on standing when it becomes alkaline. On exposure to sunlight and oxygen,blackening is accelerated. The urine will, when kept in a test tube, will start to blacken up from the top layer.

Ferric chloride test will be positive for urine and Benedict's test is strongly positive for a patient suffering from alkaptonuria.

Treatment: Diets low in Phenylalanine and Tyrosine help in reducing the levels of Homogentisic acid and decrease the amount of pigment deposited in body tissues.

Although Alkaptonuria is not life threatening,the associated arthritis may be severely crippling, bringing about a drastic change in the lifestyle of the patient.

These are a few references which I had referred for this particular module.

Thank you.