METABOLIC DISORDERS-III

PROTEIN

R.M., SRSV

INTRODUCTION

- The change in the ability of the cell to complete a particular reaction resulting in a metabolic block. If the error occurs in critical areas of energy production, the cell will die, or if the block in metabolism is in a less sensitive area the cell survives with the defect.
- Inborn Errors of Metabolism can occur in Protein Metabolism. Protein Metabolism Errors result in an amino acid that cannot be broken down. They accumulate in the body and cause toxic effects in brain development and physical growth.
- There are different diseases caused due to errors in protein metabolism. The diseases are: 1. Albinism, 2. Tyrosinosis, 3. Tyrosinemia, 4. Phenylketonuria, 5. Alkaptonuria, 6. Maple Syrup Urine Disease, 7. Hartnup's Disease, 8. Glycinuria, 9. Primary Hyperoxaluria, 10. Cystinuria, 11. Cystinosis, 12. Homocystinuria, 13. Histidinemia, 14. Isovaleric acidemia.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Albinism:-** This disease is due to lack of synthesis of pigment Melanin, which is due to defect in tyrosinase enzyme, the most responsible enzyme for Melanin bio-synthesis. It is an autosomal recessive disease with an incidence of 1 in 20,000 births.
- **Clinical features:** The ocular fundus is hypo-pigmented and iris may be grey or red. They will be associated photophobia and decreased visual acuity. The skin has low pigmentation and so skin is sensitive to UV rays. The hair is also white, Susceptibility to Parkinson's disease (as no DOPA formed), Hypopigmentation is in the form of :
- **i. Vitiligo** – loss of pigmentation around mouth, nose, eyes, nipples.
- **ii. Leukoderma** – loss of pigmentation begins with hands.
- **Treatment:** advice is for the prevention of exposure of sunlight and protection of the eyes by wearing dark glasses.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Tyrosinosis:** This syndrome is due to the absence either of hepatic p-hydroxy phenylpyruvate hydroxylase or of tyrosine transaminase activities.
- **Clinical features:** The patient excretes large quantities of tyrosine in the urine. Diet rich in tyrosine causes the excretion of other p-hydroxy phenyl acids including 3, 4 dihydroxy phenylalanine (dopa) and p-hydroxy phenyl lactic acid.
- **Treatment:** Diet low in Tyrosine, Phenylalanine are recommended.
- **Tryosinemia:**- It results due to loss of Tyrosine transaminase which is required for the degradation of Tyrosine.
- **Clinical features:** Hepatic dysfunction, cirrhosis, Liver failure, Hyperkeratosis.
- **Treatment:** Diet low in Tyrosine, Phenylalanine are recommended.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Phenylketonuria:-** Enzyme defect in Phenylalanine/tyrosine degradation leading to metabolic disorder. Here, the deficiency of hepatic enzyme Phenylalanine Hydroxylase, results in accumulation of Phenylalanine. It is an autosomal recessive condition with an incidence of 1 in 10,000 births.
- **Biochemical abnormalities:-** Phenyl alanine could not be converted to tyrosine. So phenylalanine accumulates in blood, alternate minor pathways are opened, phenyl ketone, phenyl lactate, phenyl acetate are excreted in urine.
- **Oral manifestations:** Prominent cheek and jaw bones, Widely spaced teeth, Poor development of tooth enamel. Patients are susceptible to tooth wear(erosion). Phenyllactic acid in sweet may lead to mousy body odour.
- **Clinical manifestations:** Mental retardation due to its accumulation (this maybe because, phenylalanine interferes with neurotransmitter synthesis). Hypopigmentation of hair and skin (explained by the inhibition of tyrosinase), Failure to walk/talk, growth failure.
- **Treatment:** Diet low in phenylalanine, diet with sufficient amount of tyrosine (to compensate for its absence) is recommended.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Alkaptonuria:-** Alkapton (Black colur), It is due to absence of Homogentisate oxidase activity which is necessary for breakdown of Homogentisic acid. Homogentisate accumulates in tissues and excreted in urine. It is an autosomal recessive condition with an incidece of 1 in 2,50,000 births.
- **Clinical features:** Dark urine, also known as Black Urine disease. Homogentistic acid urination results in blackening of urine on standing. The homogentisic acid is oxidised by polyphenyl oxidase to bezoquinine acetate, it is then polymerized to black colored alkapton bodies. Black pigments are deposited over the connective tissue, Ochronosis (alkapton deposition in bones, nose, ear, eyes, etc.), including joint cavities to produce arthritis.
- **Treatment:** Not a dangerous disorder, so no specific treatment. But low protein diet with phenylalanine less than 500mg/day should be taken.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Hartnup's disease:-** It's a hereditary disorder of Tryptophan metabolism characterized by low plasma levels of Tryptophan and other neutral amino acids and their elevated urinary excretion. The urine of the patients contain significantly increased amounts of indole acetic acid as well as tryptophan.
- **Clinical manifestations:** The clinical symptoms include Dermatitis, Rash, light sensitivity, Cerebellar ataxia, Mental retardation. The pellagra like symptoms are due to the deficiency of niacin derived from tryptophan.
- **Treatment:** Dietary Niacin is given.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Primary hyperoxaluria:-** Increased excretion of oxalates observed upto 600mg/day compared to a normal of 50mg/day. Primary hyperoxaluria is due to defect in glycine transaminase coupled with impairment in glyoxalate oxidation to formate.
- **Treatment:** In vit-B6 deficiency, urinary oxalate is elevated, it can be corrected by B6 supplementation. However B6 administration has no effect on endogenous hyperoxaluria.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Maple Syrup Urine Disease:-** It's a metabolic disorder of branched chain amino acids. Enzyme defect is α-keto acid dehydrogenase, which causes a blockade in conversion of α-keto acid to the respective acyl CoA thioesters. Elevated levels of branched amino acid & their ketoacids in plasma & urine, so known as branched chain ketonuria. The urine smells like Maple syrup or Burnt sugar, hence the name .
- **Biochemical complications:** Impairment in transport of other amino acids. Protein biosynthesis is reduced. The disease results in acidosis, mental retardation, coma & finally leads to death within one year of birth.
- **Symptoms:** Lethargy, Maple syrup odour of urine, Coma, Mental retardation.
- **Treatment:** To feed with a diet having low content of branched chain amino acids.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Cystinuria:-** Characterized by increased excretion of Cystine due to defective carrier system which is normally present for re-absorption of amino acids leading to excretion of amino acids in urine. (Cystine Reabsorption carrier system in kidney Cystinuria.)
- **Clinical features:** Cystine stones in kidneys (due to its insolubility).
- **Treatment:** Aim of treatment is to increase its solubility and thus reduce stone formation in kidneys.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Homocystinuria:-** A disorder of methionine metabolism, leading to an abnormal accumulation of homocysteine and its metabolites in blood and urine. Homocystinuria is an autosomal recessively inherited defect in the trans-sulfuration pathway (homocystinuria-I) or methylation pathway (homocystinuria-II and III).
- **Clinical features:** Thrombosis, Osteoporosis, MI, Stroke, etc.
- **Treatment:** Correct primary imbalance in metabolic relationship. Supply product of blocked primary pathway.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Histidinemia:-** It is an inherited disorder of histidine metabolism in which the amounts of histidine in the blood and urine are increased. There is also increased excretion of imidazole pyruvic acid. The metabolic block of histidine is due to the insufficient activity of hepatic enzyme, histidase which impairs the conversion of histidine to urocanic acid.
- **Symptoms:** Development of speech in this condition is retarded. Mental development is also retarded.
- Histidine excretion is also increased during normal pregnancy but not in the toxaemia of pregnancy. This increase is not due to metabolic defect.
- **Treatment:** These histidinemic patients are treated well with a diet containing protein hydro- lysate free from histidine instead of intact protein.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Isovaleric acidemia:-** People with isovaleric acidemia have Inborn error of leucine metabolism with defect in enzyme Isovaleric Co-A dehyrogenase. Health problems range from very mild to life-threatening. In severe cases, the features of isovaleric acidemia become apparent within a few days after birth.
- **Oral manifestation:** Cheesy odour in breath.
- **Treatment:** Limit intake of leucine in diet.
- **Cystinosis:-** Cystine storage disease where cystine crystals are deposited in many tissues and organs of RES .
- **Cause:** Lysosomal dysfunction.

INBORN ERRORS OF AMINO ACID METABOLISM

- **Glycinuria:-** Glycine is a non-essential optically inactive and glycogenic amino acid. Glycine is actively involved in the synthesis of many specialized products in the body(Heme, purins, creatinine).
- This is rare disorder, due to defect in the glycine cleavage system. Glycine level is increased in blood and CSF. Very high amount of glycine excreted in urine, due to defective renal reabsorption.
- **Symptoms:** Glycinuria characterized by increased tendency for formation of oxalate crystal stones.

Non-inherited Metabolic Disturbances Of Proteins

- **Protein Energy Malnutrition (PEM):-** PEM is a spectrum of diseases whose essential feature is a deficiency of protein at one end as in Kwashiorkor, and total inanition(starvation of infant due to severe and prolonged restriction of all food) at other end as in Marasmus. In the middle of spectrum, there is Marasmic Kwashiorkor in which there are clinical features of both disorders.
- Causes of PEM :- Dietary deficiency, Serious illness, Infections in babies, Low socio-economic status, Problems in mother leading to inadequate production of milk, Dietary factors like inadequate breast feeding, ignorance of weaning.

KWASHIORKOR

- **Introduction:** It's a maladaptive response to starvation due to lack of physiological adaptation to unbalanced deficiency where body utilizes proteins and conserves fat.
- **Occurrence:** Seen predominantly between 1-5 years of age
- **Causes:** Due to insufficient intake of proteins, as the diet of weaning child mainly consists of carbohydrates.
- **Biological manifestations:** Decreased plasma albumin levels, Visceral compartment is severely affected, Hypoproteinemia and hypoglycemia, Decreased level of electrolytes, Low enzyme levels, Percentage of body water is increased, Iron deficiency anaemia, Fatty liver (due to decreased synthesis of carrier proteins of lipoproteins), Hypoplastic bone marrow, Decreased immunity, Multi-vitamin deficiency.

KWASHIORKOR

- **Clinical symptoms:** Weight is about 60-80 % of normal as loss of true weight is masked by increased fluid retention, Generalized oedema (due to decreased colloidal osmotic pressure) of pitting variety, Sparing of subcutaneous fat and muscle mass as body utilizes its proteins to compensate the deficient state, Swollen abdomen, Moon face, Characteristic skin lesions with alternating layers of hyperpigmentation, desquamation, hypopigmentation; giving a flaky paint appearance. Hair changes like loss of colour or alternate bands of pale and darker colour, straightening and loss of firm attachment to scalp. Diarrhoea (due to impaired synthesis of digestive enzymes and loss of electrolytes in stools). Eyelashes give a 'Broomstick' appearance. Dehydration (due to diarrhoea and vomiting), Prone to infections, Psychomotor changes (due to cerebral atrophy).

KWASHIORKOR

- **Oral manifestations of Kwashiorkor:** Bright reddening of tongue with loss of papillae, Bilateral angular cheilosis (inflammation), Fissuring of lips, Loss of circumoral pigmentation. Crowded and rotated teeth giving an appearance of mouth full of jumbled teeth, Delayed eruption and hypoplasia of deciduous teeth. Mouths of Kwashiorkor patients have been described to be dry, dirty, caries free, easily traumatized with epithelium readily become detached from the underlying tissue, leaving a raw, bleeding surface. Incisor and molar growth is retarded. Increased acid solubility of enamel of incisors. Decreased salivary volume.
- **Treatment:** Provide adequate nutrition by dietary supplements. Restore normal body composition. Dietary support in the form of 3-4 gm protein and 200 cal/kg body weight. Cure the conditions that cause the deficiency.

MARASMUS

- **Introduction:** – Its an adaptive response to starvation ϖ Occurrence – Seen mostly in the first year of life.
- **Causes:** – Due to deficiency of calories.
- **Biological manifestations:** Serum albumin level normal or slightly decreased. Somatic compartment of proteins is lost, anemia, Multi vitamin deficiency, Immune deficiency, Hypoplastic bone marrow with increased red cell precursors.
- **Clinical symptoms:** Growth retardation due to low calorie intake. Loss of muscle mass as muscle proteins are mobilised as use for fuel to provide body with amino acids as a source of energy to compensate malnutrition. Due to muscle wasting rib cage is prominent. Subcutaneous fat is lost due to lipolysis, Lean body, so head appears too large. Body weight falls to 60 % of normal, Child looks older than his age, Weakened body is under stress. More chances of infections. Dry and baggy skin, Sparse hair and wrinkled appearance (Old man face), No oedema. Bones are prominent due to absence of fat around them, Hypotension and slow pulse.
- **Treatment:** Dietary support by giving food as proteins and supplements. Bring the child out of starvation.

KWASHIORKOR-MARASMUS

- **POINTS OF DIFFERENTIATION BETWEEN KWASHIORKOR AND MARASMUS:**
- **KWASHIORKOR:**
- 1. Malnutrition that occurs due to insufficient intake of proteins
- 2. Large belly, diarrhoea, pigmented skin, hair changes
- 3. Children of 1-5 yrs age
- 4. Weaned from mother's milk to a diet low in protein
- 5. Edema-Present (pitting type)
- 6. 60-80 % of normal body wt.
- 7. Decreased plasma albumin
- 8. Treated by High protein foods

KWASHIORKOR-MARASMUS

- **MARASMUS:**
- 1. Malnutrition that occurs due to starvation (i.e deficiency of proteins, carbs. and fats in diet
- 2. Muscle wasting, skin foldings, prominent rib cage , shrunken abdomen
- 3. Children under 1 yr
- 4. Failed breastfeeding (inadequate calorie intake)
- 5. Absent, rather wasting
- 6. Less than 60 % of normal
- 7. Normal / slightly decreased plasma albumin
- 8. Treated by a Well banced diet

GOUT

- **Introduction:** Gout is an inflammatory disease caused by deposition of monosodium urate monohydrate crystals in and around synovial joints.
- **Epidemiology:** Levels are higher are in men, increase with age and are associated with body weight.
- **Pathophysiology:** It can be due to diminished renal excretion or increased intake of red meat or over production of uric acid.
- **Clinical features:** Severe pain, Extreme tenderness, Marked swelling with overlying red shiny skin, Crystals may deposit in joints and soft tissues to produce irregular firm nodules called TOPHI.
- **Treatment:** Oral NSAIDs for pain relief, Local icepacks, Oral colchicine, Joint aspiration with intra articular steroid injection, Oral corticosteroids. Urate lowering therapy: Allopurinol drug which reduces conversion of hypoxanthine and xanthine to uric acid.

PLEASANT LEARNING

THANKS