METABOLIC DISORDERS-II

LIPIDS

R.M., SRSV

INTRODUCTION

- Lipids are fats or fat-like substances. They include oils, fatty acids, waxes, and cholesterol. If one have Lipid metabolism disorders, the person may not have enough enzymes to break down lipids. Or the enzymes may not work properly and body can't convert the fats into energy.
- They cause a harmful amount of lipids to build up in the body. Over time, that can damage body cells and tissues, especially in the brain, peripheral nervous system, liver, spleen, and bone marrow.
- Many of these disorders can be very serious, or sometimes even fatal.

Classifications

- **1. Disorders of F.A-oxidation:-**
  - A. **Defects in Beta-oxidation:-**
    - a) Sudden infant death syndrome(SIDS)
    - b) Zellweger's Syndrome
    - c) Carnitine deficiency
    - d) Carnitine palmitoyl transferase deficiency.
  - B. **Defect in Alpha-oxidation:-**
    - Refsum's disease.

Classifications

- **2) Lipid Storage diseases:-**
  - A. Niemann-pick disease
  - B. Farber's disease
  - C. Gaucher's disease
  - D. Krabbe's disease
  - E. Tay- sachs disease
  - F. Fabry's disease

Classifications

- **3) Disorders associated with Lipoprotein Metabolism:-**
  - A. **Hyper-Lipoproteinaemias :-**
    - a) Type-I: familial lipoprotein lipase deficiency.
    - b) Type-II: familial hypercholesterolaemia.
    - c) Type-III: familial dys-beta Lipoproteinaemia.
    - d) Type-IV: familial hypertriglyceridemia.
    - e) Type-V: Combined hyperlipidaemias.
  - B. **Hypolipoproteinaemia:-**
    - a) A-beta- Lipoproteinaemia.
    - b) Familial alpha-Lipoprotein deficiency (Tangier's disease).

Defects in Beta-oxidation

- **1) Sudden infant death Syndrome (SIDS):-**
- Disorder due to blockage in beta-oxidation. Unexpected death of healthy infants, usually overnight. Real cause of SIDS is not known.
- Now estimated that at least 10% of SIDS is due to deficiency of medium chain acyl-CoA dehydrogenase. Frequency- 1 in 10,000 births. More prevalence than phenylketonuria. Occurrence:- hypoglycaemia.
- **2) Zellweger's Syndrome:-**
- Also called Hepato renal syndrome. Rare inherited disorder. Due to the absence of peroxisomes and its enzymes in all tissues, fail to oxidize long chain FA in peroxisomes. As a result there is accumulation of FA C26 – C38 chain length in brain tissues and other tissues like Liver and Kidney.

Defects in Beta-oxidation

- **3) Carnitine Deficiency:-**
- It occurs in a)In newborns:- Specially premature infants, owing to inadequate synthesis or renal leakage. b) In adults:- Can occur in hemodialysis. Patients with organic acidurias, carnitine is lost in urine being conjugated with organic acid. Clinical features:- Hypoglycemia. Treatment:- oral therapy with Carnitine.
- **4) Carnitine- palmitoyl transferase deficiency:-**
- Features: a) Hepatic deficiency of the enzyme results in hypoglycaemia and low plasma ketone bodies. b) Muscular deficiency of these enzyme produces impaired FA-oxidation which results in recurrent muscle weakness and myoglobinuria.

Defects in Alpha-oxidation

- **1) Refsum's disease:-**
- Enzyme deficiency:- "Phytanate alpha-oxidase".
- Inheritance:- autosomal recessive.
- Age:- from childhood to adult life.
- Biochemical Defect:- Phytanic acid.
- Pristanic acid Accumulates in tissues & blood. Blood shows increase up to 20% of the total FA.
- Clinical manifestations:- Neurological signs & symptoms, Sensory disturbances, Eye manifestations, Mental development:- Usually normal, CS-Fluid:- Increased protein & cell count normal. Diagnosis:- Increased phytanic acid in plasma. Treatment:- Omit intake of dietary phytols which is the precursor of phytanic acid.

Lipid storage diseases

- Also known as sphingolipidoses. Genetically acquired. Group of inherited diseases that are caused by a genetic defect in the catabolism of lipids containing sphingosine. They are part of a larger group of lysosomal disorders.
- **Characteristics are:**
- a) Complex lipids containing ceramide accumulate in cells, particularly neurons, causing neurodegeneration and shortening the life span.
- b) The rate of synthesis of the stored lipid is normal.
- c) The enzymatic defect is in the lysosomal degradation pathway of sphingolipids.
- d) The extent to which the activity of the affected enzyme is decreased is similar in all tissues.

Lipid storage diseases

- **1) Niemann-Pick disease:-** Sphingomyelin, Ceramide accumulation caused by deficiency of sphingomyelinase. Principal storage substance: sphingomyelin which accumulates in reticuloendothelial cells. Liver and spleen enlargement, mental retardation.
- **2) Fabry's disease:-** Caused by deficient in lysosomal α-galactosidase. Accumulation of ceramide trihexoside in kidneys of these patients. Sometimes referred to as ceramide trihexosidase. Skin rash, kidney failure, pains in the lower extremities-Painful & deformed joints. Now treated with enzyme replacement therapy: agalsidase beta.

Lipid storage diseases

- **3) Gaucher's disease:-** Glucocerebroside, Ceramide accumulation caused by a deficiency of lysosomal glucocerebrosidase. Increase content of glucocerebroside in the spleen and liver. Erosion of long bones and pelvis. Enzyme replacement therapy is available for the Type I disease (Imiglucerase), Also miglustat– an oral drug which inhibits the enzyme glucosylceramide synthase, an essential enzyme for the synthesis of most glycosphingolipids.
- Hepatomegaly, Splenomegaly, Osteoporosis & mental retardation.

Lipid storage diseases

- **4) Krabbe's disease:-** Galactocerebroside Ceramide accumulation, Also known as globoid leukodystrophy. Caused by a deficiency in the lysosomal enzyme galactocerebrosidase, Increased amount of galactocerebroside in the white matter of the brain. Absence of Myelin formation, Hepatomegaly, Splenomegaly & mental retardation.
- **5)Tay-Sachs disease:-** A fatal disease which is due to the deficiency of hexosaminidase-A activity. Accumulation of ganglioside GM2 in the brain of infants. Mental retardation, blindness, inability to swallow. A "cherry red " spot develops on the macula (back of the eyes). Tay-Sachs children usually die by age 5 and often sooner. Blindness, mental retardation, death within 2-3yrs.

Disorders associated with Lipoprotein Metabolism

- **A. Hyper-lipoproteinaemia:-**
- **Type-I:** familial lipoprotein lipase deficiency:-
- Rare disorder characterized by hyper-triglyceridaemia & hyperchylomicronaemia. VLDL(Pre-beta Lipoproteins) also increased. Alpha Lipoprotein(HDL) & Beta-Lipoproteins(LDL) is decreased. Inheritance:- Autosomal recessive. Enzyme deficiency:- "Lipoprotein lipase"
- Clinical features:- Recurrent abdominal pain. Eruptive xanthomas. Hepatomegaly.
- **2) Type-II:** familial hyper-cholesterolaemia (FHC):-
- Common disorder. Characterized by:- Increased Total Cholesterol & HDL. May be high TG & VLDL. Inheritance:- Autosomal dominant Frequency:- 1:500(0.2%) Metabolic defect:- No enzyme deficiency but defect of LDL receptors.
- Clinical features:- Atherosclerosis.

Disorders associated with Lipoprotein Metabolism

- **3) Type-III:** familial dys-beta Lipoproteinemia:-
- Synonyms:- Broad beta disease & Remnant removal disease. Characterised by:- Increased LDL & VLDL. Rise in IDL, Hypercholesterolemia & hypertriglyceridemia, Inheritance:- Autosomal dominant, Frequency:- 1:5000(0.02%), Metabolic defect:- Increased apo-E & apo-B Conversion of normal VLDL to IDL & its degradation without conversion of LDL. Defect is in "Remnant" metabolism.
- Clinical Features:- Palmar xanthoma. High incidence of vascular disease.

Disorders associated with Lipoprotein Metabolism

- **4) Type-IV:** familial hypertriglyceridemia:-
- Characterised by:- Increased TG & VLDL. Cholesterol may be normal or increased. Decreased HDL & LDL. Inheritance:- Autosomal dominant Metabolic defects:- over production of VLDL & Apo-CII. Clinical features:- Associated with diabetes mellitus, IHD & Obesity.
- **5) Type-V:** Combined hyperlipidaemias:-
- Hypercholesterolemia & hypertriglyceridemia. Decreased HDL & LDL. Inheritance:- Autosomal dominant. Metabolic defects:-Secondary to other causes. Clinical features: Manifested only in adulthood. Xanthomas, Abnormal glucose tolerance. Frequency Associated with diabetes mellitus & Obesity.

Disorders associated with Lipoprotein Metabolism

- **B)Hypolipoproteinaemia:-**
- **1) A-Beta Lipoproteinaemia:-** Rare inherited disorder. Characterized by:- Decreased plasma cholesterol due to absence of LDL. Low TG. No Chylomicrons & VLDL formed. Clinical features:- Malabsorption. Mental & physical retardation. Acanthocytosis. Metabolic defect:- Defect in "Synthesis of apo-B" leading to gross deficiency of apo-B resulting to deficiency of lipoproteins containing apo-B i.e mainly Chylomicrons, VLDL & LDL.
- **2) Familial Alpha-Lipoprotein deficiency:-** Also called Tangier's disease Characterized by:- Deficiency of HDL. In homozygous patients plasma HDL may be nearly completed absent. Inheritance:- Autosomal recessive, Metabolic defect:- Reduction in apo-AI & apo-AII, Leading to accumulation of cholesteryl esters in diff. tissues. Clinical features- ¬ Increased risk of CAD. Adenoids.

...LEARNING...

IS

GREAT

THANKS