Unit-III

Major Metabolic disorders and its causes

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Metabolic Errors

- Metabolic errors are also referred to as congenital metabolic diseases or inherited metabolic diseases.
- The term ‘inborn errors of metabolism’ known as (IEM), are a diverse group of diseases that result from perturbations of biochemical pathways.
- IEM have traditionally been regarded as Mendalian traits; however it is now increasingly recognised that they represent the best examples of complex gene-environment interactions and more specifically, gene-nutrient interactions that lead to complex disease.
- IEM could be a powerful tool for dissecting both monogenic and common multifactorial diseases.

- IEM are characterised by dysregulation of the metabolic networks that underline development and homeostasis, and constitute an important and expanding group of genetic disorders in human.
- IEM was first coined by a British physician Archibald Garrod (1857-1936) to describe the hereditary deficiency or alteration in enzyme reactions in early 20^{th} century.
- These results in substrate accumulation causes minor to severe clinical symptoms, mostly with neurological and psychiatric symptoms that often leads to death or life long disability.

- Although IEM have usually been considered paediatric diseases, they can be present at any age.

- Effective therapy of IEM requires the alterations of metabolite flux. This can be achieved by reducing pathway precursors, restoring adequate biochemical activity or diverting metabolites to alternative pathways.

Traditional Diagnosis Methods

- Traditionally the IEM are categorised as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, or lysosomal storage disease.
- Diagnostically these metabolic disorders can be divided into 5 groups as-
- (a)Energy metabolism disorder: disorders of respiratory chain, pyruvate dehydrogenase, GLUT1, fatty-acid 5 β-oxidation, and key cofactor such as electron transfer flavoprotein, thiamine, biotin, riboflavin, vitamin E and coenzyme.
- (b)Intoxication syndrome: porphyrias, urea-cycle defect, homocystinurias, organic acidurias and amino acidopathies.

- (c)Lipid-storage disorder: lysosomal storage disorder (Krabbe disease, Metachromatic leukodystrophy, Gaucher's disease), peroxisomal disorders (disorders of pristanic acid metabolism, peroxisome biogenesis disorder).
- (d)Metal-storage diseases (such as iron, copper and manganese).
- (e)Neurotransmitter metabolism defects (serotonin, dopamine and glycine).

•Mainly metabolic disorders are of 3 types-

- Type 1: Silent Disorders
- Type 2: Acute Metabolic Crisis.
- Type 3: Neurological Deterioration

Type 1:Silent Disorders

✓Do not manifest life-threatening crises.

✓Untreated could lead to brain damage and developmental disabilities.

Eg. Phenylketonuria.

Type 2:Acute Metabolism Crisis

✓Life threatening in infancy.

✓Children are protected in utero by maternal circulation which provide missing product or remove toxic substance.

Eg. Urea cycle disorder.

Type 3:Progressive Neurological Deterioration

Eg. Tay sachs disease, Gaucher disease, Mitochromatic leukodystrophy

✓DNA analysis show: mutations.

✓Nonfunctioning enzyme results:-

Early Childhood- progressive loss of motor and congitive skills.

Pre-school- non responsive state.

Adolescence- death.

- With the identification of specific enzymes and metabolic pathways, metabolic diseases can be diagnosed in many cases with routine biochemical blood tests and metabolic screening of urine, such as ferric chloride test, DNPH test, Rothera's test, Cetavlon test, Cyanide nitroprusside test etc.

- However, the complete characterisation of the particular condition usually involves more specific studies, such as enzyme assays, DNA analysis and family studies.

- To recognize a metabolic disorder there are 2 ways-

•Index of suspicion

- Eg. "With any full-term infant who has no antecedent maternal fever or PROM-simple lab tests.

•Simple Lab tests

✓ Glucose, Electrolytes, Gas, Ketones, BUN, Creatinine.

✓Lactate, Ammonia, Bilirubin, LFT.

✓Amino acids, Organic acids, Reducing substances.

Index of Suspicion

- Family History
- History
- Physical Examination
- General
- H&N
- CNS
- Respiratory
- CVS
- Abdominal
- Skin

Laboratory Test

- Anion Gap Metabolic Acidosis/Normal
- Respiratory alkalosis
- Low BUN relative to creatinine
- Hypoglycaemia
- Especially with hepatomegaly(enlarged liver)
- Non-ketotic

In Neonates-

- Acute life threatening illness.
- Encephalopathy
- Vomiting
- Respiratory
- Seizures, Hypertonia
- Hepatomegaly
- Hepatic dysfunction
- Odour, dysmorphism, FTT (Failure to thrive), hiccoughs.

- Now a days tandem MS(TM) has become a key technology in field of neonatal screening for detection of more than 20 inherited disorders of amino acids, fatty acids and organic acid metabolism from a single dried blood spots.

Synopsis of Diseases due to Genetic Disorder

- Many human diseases have a genetic components. Some of these conditions are under investigation by researchers at or associated with National Human Genome Research Institute (NHGRI) .

- A genetic disorder is a disease caused in whole or in part due to cause of mutations in the DNA sequence away from the normal sequence.

- Genetic disorders can be caused by a mutation in 1 gene (monogenic), by multiple genes, by combination of gene mutations and environmental factors, or by damage to chromosomes.

- As by the research the secrets of human genome, many mysteries are unlocked and reveals that nearly all diseases have some or the another connections with a genetic components.

- Some diseases are caused by mutations which either inherited by parents or other may caused by acquired mutations in a gene/ group of genes in a person's lifetime, which occurs either randomly or due to some environmental exposures. It may include cancers, as well as forms of neurofibromatosis.

List of Genetic Disorders

- Achondroplasia
- Gaucher Disease
- Hemochromatosis
- Haemophilia
- Myotonic Dystrophy
- Neurofibromatosis
- Osteogenesis Imperfecta
- Retinitis Pigmentosa

Cancer

- Cancer is the uncontrolled growth of abnormal cells anywhere in a body. These abnormal cells are termed as cancer cells, malignant cells or tumour cells.

- Anything that may cause a normal body cell to develop abnormally potentially can cause cancer related or causative agents are:

- Chemical or toxic compound exposures
- ionising radiations
- some pathogens
- human genetics.

- Cancer symptoms and signs depend upon the type and grade of cancer, and general signs and symptoms are not specific.

- There are many tests to screen and presumptively diagnose cancer, the definite diagnosis is made by examination of a biopsy sample of suspected cancer tissue.

- Cancer staging is often determined by biopsy results and helps determining the cancer type and the extent of cancer spread. With this prognosis of cancer can be ranged from excellent to poor.

- Many cancers are not only confined to humans, animals and other living organisms can also get cancer.

- Cancer cells leaving an area and travel through the blood and lymph system and lodge in other organs and growing in another body area is termed metastatic spread or metastasis.

Different types of Cancer

There are over 200 types of cancers. General categorization of specific types of cancers are-
Carcinoma
Sarcoma
Leukaemia
Lymphoma & Myeloma
CNS Cancers

3 most common cancers predominant in men, women and children are-
Men- Prostrate, lings and colorectal.
Women- Breast, lungs and colorectal.
Children- Leukaemia, brain tumours and lymphoma.

The incidence of cancer and its types are influenced by many factors such as age, gender, race, local environmental factors, diet and genetics.

Genetics of Cancer

- All cancer begin when 1 or more genes in a cell mutate. It creates an abnormal protein. Or it may prevent a protein's formulation.

- An abnormal protein provides different information than a normal protein. This can cause cells to multiply uncontrollably and become cancerous.

- Factors responsible for mutations are- tobacco, UV radiations, viruses, age,etc.

- Germline mutations are less common. These are the inherited cancers which can pass from generation to generation as mutation occurs in a sperm/egg cell so it passes at the time of conception to the embryo and gets copied into every cell . It accounts for about 5-20% of all cancers.

Oncogenes

- An oncogene is a gene that has the potentiality to cause cancer. These genes turn a healthy cell into cancerous cells.

- In tumours these genes are often mutated or expressed at high levels. Mutations in these genes to get inherited are unknown.

- The resultant protein encoded by an oncogene is termed oncoprotein. Some oncoproteins are accepted and used as tumour markers.

- 2 common oncogenes are-

•**HER2**, A specialised protein that controls cancer growth and spread. It is found in some cancer cells. E.g. Breast and ovarian cancer cells.

•**RAS family of genes,** which makes proteins involved in cell communication pathways, cell growth, and cell death.

Tumour Suppressor Genes

- Tumour suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die.
- When tumour suppressor gene don’t work properly, cell can grow out of control, which can lead to growth of cancerous cell.
- It normally keeps the cell from dividing too quickly, when something goes wrong with the genes, such as a mutation, cell division can go out of control and eventually form tumours.
- Tumour suppressor genes cause cancer when they are inactivated. Mostly these gene mutations are acquired, not inherited.
- E.g. **BRCA1**, **BRCA2** and **P53** or **TP53**.

Thank You…