Inborn Errors of Metabolism

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Abstract: Inborn errors of metabolism (IEMS) are due to congenital metabolic disorders. They are caused by defects related to synthesis, metabolism and storage of biochemical compounds. Sudden illness, nonspecific features like poor feeding, lethargy, vomiting, failure to thrive, apnea, organomegaly are the features. In acute presentation the disorder appear normal at birth but in chronic presentation the disorder appear from birth to adult hood.

Based on the pathophysiology IEMS are classified into intoxication group which include phenylketonuria, alkaptonuria, Duchenne muscular dystrophy and thalassemia. Energy metabolism group which include mitochondrial disorders and complex molecule group which includes Gauchers disease, Tay sachs disease, Niemann pick disease, their clinical features, diagnosis and treatment.

I. Introduction

Inborn errors of metabolism (IEMS) are conditions caused by genetic defects related to synthesis, metabolism, transfer or storage of biochemical compounds metabolic error usually results in the deficiency of one or more enzymes requires for the formation or transport of proteins.

Suspecting an inborn error of metabolism:
Inborn errors of metabolisms (IEMS) may present in the newborn period early childhood or in adults. The diagnosis is often delayed, and requires a high index of suspicion, since symptoms are nonspecific.

Features of metabolic disorders:
1. Sudden and rapid illness in a previous normal baby precipitated by fever, vomiting or fasting.
2. Non specific features like poor feeding, lethargy, vomiting, hypotonia, hiccups, respiratory abnormalities, bradycardia.
3. Rapidly progressive encephalopathy of unknown etiology.
4. Organomegaly
5. Persistent hypoglycaemia, intractable metabolic acidosis, unexplained leukopenia or thrombocytopenia.
6. Family history of unexplained neonatal deaths or progressive neurological disease.
7. Parental consanguinity.

Presentation of disease:
There are two types of presentations. They can be acute or chronic presentation.

1. Acute Presentation:
Neonates with metabolic disorders appear normal at birth since the small intermediary metabolites are eliminated by the placenta during foetal life. Disorders of glucose, protein and fat break down usually present early although premature neonates with transient hyperammonemia of new born than the term babies with glutaric acidemia type III disease may present an the first day of life. In general early onset of clinical symptoms is associated with severe disease then the late onset with milder forms.

Chronic and progressive presentation:
This group of metabolic disorders is characterized by variable but insidious onset from birth to adult hood. Unexplained developmental delay with or without seizures, organomegaly, cataract, dislocated lens, abnormal urine and failure to thrive are important clues.

Classification:
Based on the pathophysiology, IEMs can be classified as follows:
1) **Intoxication group**: It includes disorders of intermediary metabolism, with accumulation of toxic compounds resulting in acute or progressive symptoms. Amino acidopathies Ex. Phenylketonuria and maple syrup urine diseases, organic aciduria, alkaptonuria, thalassaemia etc.,

1) **Phenylketonuria**: Phenylketonuria is a disorder of phenylalanine metabolism and occurs due to phenylalanine hydroxylase.

**Clinical features:**
Affected individuals have profound and irreversible intellectual disability, microcephaly, epilepsy and behavioural problems. These patients often have a musty body odor and skin conditions as eczema caused by excretion of excessive phenylalanine. Decreased skin, hair and eye pigmentation may also be present due to associated inhibition of tyrosinase and reduced melanin synthesis.

![Phenylketonuria (PKU)](image)

**Diagnosis:**
1. New born screening such as Guthrie card bacterial inhibition assay (BIA), flurometric analysis and tandem mass spectrometry.
2. Molecular genetic testing of phenyl alanine hydroxylase (PAH) gene.

**Treatment:**
A low protein diet and use of phenylalanine free medical formula soon after birth to achieve plasma concentration 120 to 360 µmol (2-6 mg/dl) is recommended.
PKU may benefit from adjuvant therapy with single daily dose of 5-10 mg/kg tetrahydrobiopterin.

**Alkaptonuria:**
This is the 1st inborn error of metabolism described by Garrod in 1902 caused by defect of the enzyme homogentisic acid oxidase.

**Clinical features:**
The disorder comes to attention due to change in color of urine to brownish black or staining of diapers. Pigment deposits initiate articular cartilage, resulting in degeneration and osteoarthritis inter vertebral discs are degenerated, arthritis of shoulders and hips. Pigment deposits in kidney manifest renal stones. Grayish discoloration of ear and nose cartilages after 30 years.

**Diagnosis:**
PH of urine is alkaline organic acid analysis can identify homogentisic acid.

**Treatment:**
No treatment, administration of vitc prevents deposits in cartilages. Nitisinone inhibits homogentisic acid may prove useful.

**Thalassemia:**
A blood disorder involving lower amounts of oxygen carrying protein. It is caused due to defects in globin chain of haemoglobin.

**Clinical symptoms:**
The common symptoms are anaemia fatigue, weakness, failure to thrive, iron overload, pallor, shortness of breath and yellow skin and eyes.
Diagnosis:
It is diagnosed by haemoglobin electrophoresis and genetic testing.

Treatment:
Severe forms require blood transfusions (or) donor stem cell transplant.

**Duchenne muscular dystrophy (DMD):**
DMD is a genetic disorder characterized by progressive muscle degeneration and weakness. It is one of the nine types of muscular dystrophy caused by the absence of dystrophin a protein that helps keep muscle cells intact.

Clinical symptoms:
Abnormality in walking, difficulty standing, muscle weakness, loss of muscle difficulty in swallowing, scolisis etc.,

Diagnosis:
Elevated creatine kinase in blood progressive symmetrical muscle weakness. Being an x-linked disorder it mainly effects boys. Multiple ligation dependent probe amplification (MLPA) is best diagnosis.

Treatment:
No cure but physiotherapy and corticosteroids can help.

**II. Defects in energy metabolism:**
It include deficient energy produced within liver, muscle, heart and brain Ex. Mitochondrial disorders, disorders of glycolysis, gluconeogenesis and hyperinsulinism.

**Mitochondrial defects:**
Fatty acid oxidation plays a major role in energy production during fasting (or) periods of high energy demand leading to glycogen depletion. It involves three processes.
a) Mobilization of fatty acids into mitochondria.
b) β Oxidation.
c) Electron transfer to the respiratory chain.
The defects in any one of these processes causes disease.

Clinical features:
Symptoms are precipitated by fasting, exercise or intercurrent illness leading to episodes of metabolic decompensation.
1) Presence of acute hypoketotic hypoglycemia and encephalopathy associated with reye like illness hepatomegaly and liver dysfunction.
2) Cardiomyopathy and conduction defects including arrhythmias causing sudden early death.
3) Myopathy.

Diagnosis:
This is usually made by performing organic analysis or urine and plasma acylcarnitine probe which is later confirmed by enzyme assay, or mutation analysis.

Treatment:
Prolonged fasting should be avoided. Medium chain triglyceride rich formula can be given in VLCAD LCHAD and CPT I and II deficiency but not in MCAD and MAD deficiency.

**III. Disorders of Complex molecules**
It include lysosomal storage diseases peroxisomal disorders, congenital disorders. The symptoms are progress and permanent.
1) **Gaucher disease:**
Gaucher disease is the commonest lysosomal storage disorder inherited in an autosomal recessive manner. It is due to the deficiency of glucocerebrosidase, that splits glucose from glucosylceramide resulting in the accumulation of cerebroside in reticuloendothelial system. These cells are large eccentric nuclei with vacuolated cytoplasm and “wrinkled tissue paper appearance” (Gaucher cells).
Clinical symptoms:
The spleen shows signs of hypersplenism. Ex. Lackopenia and thrombocytopenia. The liver is enlarged and marrow cavity is widened due to deposits of Gaucher cells. Expansion of bone marrow at the ends of femur and humerus.

Diagnosis:
Measuring glucosidase levels in leukocytes serum chilotriosidase levels are elevated EEG and neuropsychometry is required. MRI and ultrasound of spleen and liver. DNA analysis and parental diagnosis.

Treatment:
This was 1st storage disorder for which treatment is available. Enzyme replacement therapy (ERT) and substrate reduction therapy.

2) Tay-sachs disease:
It is an autosomal recessively inherited defect. Deficiency of hexosaminidase leads to accumulation of ganglioside GM₂ within ganglion cells of the nervous system. Myelin is degenerated.

Clinical symptoms:
The child progressively becomes spastic, blind and demented. Fundus shows cherry red spot over the macular region. In sandhoff disease visceral involvement is present in addition to tay-sachs disease.

Diagnosis:
It manifests in 6 months. Diagnosis involves blood test that contain very low. β hexosaminidase A enzyme. Molecular genetic testing of HEXA gene.

Treatment:
No treatment.

3) Niemann pick disease:
It is autosomal recessive disorder of sphingomyelin and cholesterol in the lysosomes.

Clinical features:
They begin early life with feeding difficulties, failure to thrive, development delay and neuroregression. There is protruberent abdomen with hepatosplenomegaly and sphingolipidosis.
Diagnosis:
Cherry red spot in fundus in half of the cases measurement of sphingomyelinase levels.
Type B has milder heterosplenomegaly
Type C is associated with extra pyramidal manifestations.

Treatment:
No treatment.

Reference books