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An Overview: Inborn Error of Metabolism

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ARTICLE ID: 006

Introduction

Inborn error of metabolism are a large group of hereditary biochemical diseases in which specific gene mutation cause abnormal or missing proteins that lead to alter function. Inborn errors of metabolism occur from a group of rare genetic disorders in which the body cannot metabolize food components normally. Food not broken down properly may produce chemicals that build up in various parts of the body causing medical problems and learning disorders. Although any inborn error of metabolism is very rare, as a group, inborn errors of metabolism occur in 1 in 2500 births. They can present at any age. Thus, awareness of these diseases, their evaluation is critical for the emergency provider. The term "Inborn error of metabolism" was first coined by British Physician Archibald Garrod in 1908. He dealt with four specific metabolic disorders- albinism, cystinuria, pentosuria and alkaptonuria.

Common characteristics features of IEM –

1) Inheritance of inborn errors of metabolism

- Most of the inborn errors of metabolism are inherited as: Autosomal recessive.
- There are also X-linked and mitochondrial inherited. A few are inherited as autosomal dominant.

2) Racial and ethnic groups

- The incidence varies with predominance of certain inborn errors of metabolism within particular groups.
- Some of these diseases occur in large numbers in communities in which consanguinity is common.

Classification of IEM-

Inborn error of metabolism is mainly categorized depending on their onset, primary signs and symptoms, organ/systems affected and disease presentation (acute/chronic). IEM were classified as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism or lysosomal storage diseases. Some of the major classes of congenital

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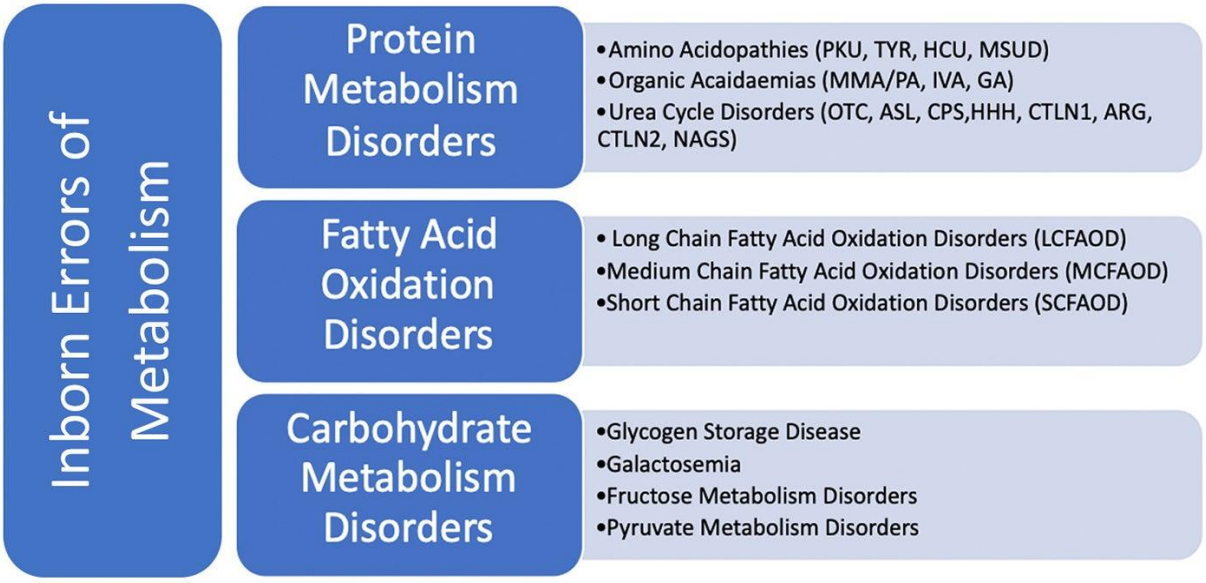
diseases are as follows:



Galactosemia

Galactosemia is a metabolic condition in which the body cannot breakdown galactose (sugar found in milk) due to the deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT).Galactosemia is an inherited disorder. This means if both parents carry non working copy of gene that can cause Galactosemia, each of their children has 25% chance of being affected with it. People with Galactosemia are unable to fully breakdown the simple sugar galactose.

If infants with Galactosemia are given milk (human or animal), galactose gets accumulated in their system and damages the liver, brain, kidneys and eyes. This causes jaundice, vomiting, grow the failure and other complication including liver failure resulting in death in infancy. There is no cure for Galactosemia.

Therefore, people with Galactosemia must be careful about eating other foods containing galactose or by removing lactose from the diet.

Phenylketonuria

Phenylketonuria (PKU) is a rare condition which is caused due to the deficiency of the enzyme phenylalanine hydroxylase (PAH), which is essential for the breakdown of the amino acid phenylalanine. Incidence of PKU is 1 in 10,000 to 15,000 newborns.When PAH deficient, phenylalanine is accumulates and is converted into phenylketones, which are detected in the urine. The first newborn screening was developed in 1959. If children with

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PKU consume food high in protein content, phenylalanine stores in their body, which causes severe brain damage and central nervous system which leads to intellectual disability, neurological and behavioral problems.There is no cure for PKU. However, it can be controlled by diet. Patients with PKU should follow diet low in phenylalanine and high in tyrosine can be very effective treatment. Supplements are also available in market for PKU like kuvan, metanutrition.

Gaucher's Disease

Gaucher's disease is a rare genetic disorder that results in a build up of certain fatty substances in certain organs, especially spleen and liver. This causes these organs to enlarge and can affect their function. The fatty substances can also help in build up bone tissue, weakening the bone and increasing the risk of fractures. If the bone marrow is affected, it can inhibit the blood's ability to clot. An enzyme that breaks down these fatty substances does not work properly in people with Gaucher's disease.

Causes-

Gaucher's disease is passed along in an inheritance pattern called autosomal recessive. Both parents must be carriers of gaucher mutated gene for their child to inherit the condition.

Symptoms-

Most people who have Gaucher's disease have following symptoms:

- **Abdominal complaints**. Due to enlargement of liver and especially spleen, the abdomen can become painfully distended.
- **Blood disorder**. Severe fatigue caused by the decrement in healthy RBCs. It also affects the cells which cause easy bruising and nosebleeds.
- **Skeletal abnormalities.** Gaucher disease can weaken bone, increasing the risk of painful fractures.More rarely, Gaucher disorder affects the brain, which can cause abnormal eye movements, swallowing difficulties, muscle rigidity and seizures.

Diagnosis-

A person with Gaucher disorder typically requires regular tests to track its progression including:

Lab Test-

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Blood samples can be checked for levels of the enzyme associated with Gaucher disease.

Imaging Test-

- Dual energy X-ray absorptiometry (DXA). This test uses low-level X-rays to measure bone density.
- MRI. Using radio waves and a strong magnetic field, an MRI can show whether the spleen or liver is enlarged and if bone marrow has been affected.

Treatment-

While there is no cure for Gaucher's disease, a variety of treatments can help controlling the Gaucher's disease, some of them mention below:

- Enzyme replacement therapy.
- Miglustat (Zavesca)
- Osteoporosis drugs
- Eliglustat (Cerdelga)

Symptoms of IEM-

The symptoms and signs depend on metabolic problem associated with the condition. Some common symptoms of inherited metabolic disorders include:

1. Vomiting
2. Poor appetite
3. Weight loss
4. Hypothermia
5. Jaundice
6. Abnormal odor of urine, breath, saliva or sweat
7. Coma
8. Lethargy

Diagnosis-

With the recognition of specific enzymes and metabolic pathway, dozens of congenital metabolic diseases can be diagnosed in many cases with routine biochemical blood tests and metabolic screening of urine, such as DNPH test, Rothera's test, Ferric chloride test, Catavlon test, Cyanide nitroprusside test etc.

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Although, the complete characterization of particular condition generally, involves more specific studies like enzyme assays, DNA analysis, skin or tissue biopsy and family studies.

These days, Tanden mass(TM) spectrometry has become essential or central technology in the field of neonatal screening that allows detection of more than 20 inherited disorders of amino acid, fatty acid and organic acid metabolism from a single dried blood spot. It has replaced classic screening techniques of one-metabolite, one-analysis, one-disease with one analysis, many- metabolites and many diseases. With the advancement of technology, traditional electrospray tandem mass spectrometry screening is now being extended to nanospray ionization and high resolution mass spectrometry, allowing the selective detection of more than 400 individual metabolic constituents of blood [Julia Denes, Eszter Szabo, L.Robinette *et al,* 2012]. Inborn errors of metabolism can be diagnosed prior to the manifestation of symptoms or after the manifestation of symptoms.

Newborn Screening-

Newborn screening (NBS) is a protocol devised diagnoses IEM in asymptomatic infants to prevent severe damage to the child's organ. The ultimate goal of NBS is to reduce mortality and morbidity from the disorders. PKU was the first disorder or which a screening test developed in 1960, some people still cal the newborn screen "the PKU test".

Screening is done using the following methods:

1. Blood test- a few drops of blood are taken from the baby's heel. The blood is sent to a lab for analysis.
2. CCHD test- a provider will place a small soft sensor on the baby' skin and attach it to a machine called an oximeter for a few minutes. The oximeter will measure the baby's oxygen level in the hand and foot.
3. Hearing test- a health care provider will place a tiny earpiece or microphone in the infant's ear.

Treatment-

The treatment of IEM aims at limiting the toxicity of substrates in cells. If this is done at an early stage of the condition, major complications, such as developmental delay can be prevented.The following methods help treat inherited metabolic disorders:

1. Including special diets to eliminate the intake of food that cannot be metabolized.

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2. Removal of toxic chemicals accumulated in the body by treating the blood with purifying chemicals.
3. Replacing the missing or inactive enzymes with an enzyme supplement or other supplements to restore the body's metabolism.

Gene therapy also has a role in the treatment of these disorders, where the mutated gene can be supplemented by normal genes that can produce the enzyme.

Conclusion

IEM are individually rare but collectively numerous, causing substantial morbidity and mortality. In India, these are limited published studies on the newborn population screening MSUD, PKU, hyperglycinemia; hypothyroidism and G6PD deficiency were found to be the common errors in one NBS pilot project in Karnataka. Another pilot program from Hyderabad revealed a high prevalence of CH (1 in 1,700) followed by congenital adrenal hyperplasia. Though a very high prevalence of IEM to the extent of 1 in every 1,000 newborn was observed in several hospital based study, but no study truly reflected the extent of the IEM in India. These result in psychosocial crises that challenge individual and family modes of functioning across the life cycle. The most important is to get the government's policy and financial support for expended screening.

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