WebMD

Inherited Metabolic Disorders

Inherited metabolic disorders are genetic conditions that result in metabolism problems. Most people with inherited metabolic disorders have a defective gene that results in an enzyme deficiency. There are hundreds of different genetic metabolic disorders, and their symptoms, treatments, and prognoses vary widely.

What Is Metabolism?

Metabolism refers to all the chemical reactions taking place in the body to convert or use energy. A few major examples of metabolism include:

- Breaking down the carbohydrates, proteins, and fats in food to release energy.
- Transforming excess nitrogen into waste products excreted in urine.
- Breaking down or converting chemicals into other substances and transporting them inside cells.

Metabolism is an organized but chaotic chemical assembly line. Raw materials, half-finished products, and waste materials are constantly being used, produced, transported, and excreted. The "workers" on the assembly line are enzymes and other proteins that make chemical reactions happen.

Causes of Inherited Metabolic Disorders

In most inherited metabolic disorders, a single enzyme is either not produced by the body at all or is produced in a form that doesn't work. The missing enzyme is like an absentee worker on the assembly line. Depending on that enzyme's job, its absence means toxic chemicals may build up, or an essential product may not be produced.

The code or blueprint to produce an enzyme is usually contained on a pair of genes. Most people with inherited metabolic disorders inherit two defective copies of the gene -- one from each parent. Both parents are "carriers" of the bad gene, meaning they carry one defective copy and one normal copy.

In the parents, the normal gene copy compensates for the bad copy. Their enzyme levels are usually adequate, so they may have no symptoms of a genetic metabolic disorder. However, the child who inherits two defective gene

copies cannot produce enough effective enzyme and develops the genetic metabolic disorder. This form of genetic transmission is called autosomal recessive inheritance.

The original cause of most genetic metabolic disorders is a gene mutation that occurred many, many generations ago. The gene mutation is passed along through the generations, ensuring its preservation.

Each inherited metabolic disorder is quite rare in the general population. Considered all together, inherited metabolic disorders may affect about 1 in 1,000 to 2,500 newborns. In certain ethnic populations, such as Ashkenazi Jews (Jews of central and eastern European ancestry), the rate of inherited metabolic disorders is higher.

Types of Inherited Metabolic Disorders

Hundreds of inherited metabolic disorders have been identified, and new ones continue to be discovered. Some of the more common and important genetic metabolic disorders include:

Lysosomal storage disorders : Lysosomes are spaces inside cells that break down waste products of metabolism. Various enzyme deficiencies inside lysosomes can result in buildup of toxic substances, causing metabolic disorders including:

- Hurler syndrome (abnormal bone structure and developmental delay)
- Niemann-Pick disease (babies develop liver enlargement, difficulty feeding, and nerve damage)
- Tay-Sachs disease (progressive weakness in a months-old child, progressing to severe nerve damage ; the child usually lives only until age 4 or 5)
- Gaucher disease (bone pain, enlarged liver, and low platelet counts, often mild, in children or adults)
- Fabry disease (pain in the extremities in childhood, with kidney and heart disease and strokes in adulthood; only males are affected)
- Krabbe disease (progressive nerve damage , developmental delay in young children; occasionally adults are affected)

Galactosemia: Impaired breakdown of the sugar galactose leads to jaundice, vomiting, and liver enlargement after breast or formula feeding by a newborn.

Maple syrup urine disease: Deficiency of an enzyme called BCKD causes buildup of amino acids in the body. Nerve damage results, and the urine smells like syrup.

Phenylketonuria (PKU): Deficiency of the enzyme PAH results in high levels of phenylalanine in the blood. Mental retardation results if the condition is not recognized.

Glycogen storage diseases: Problems with sugar storage lead to low blood sugar levels, muscle pain, and weakness.

Mitochondrial disorders: Problems inside mitochondria, the powerhouses of cells, lead to muscle damage.

Friedreich ataxia: Problems related to a protein called frataxin cause nerve damage and often heart problems. Inability to walk usually results by young adulthood.

Peroxisomal disorders: Similar to lysosomes, peroxisomes are tiny spaces filled with enzymes inside cells. Poor enzyme function inside peroxisomes can lead to buildup of toxic products of metabolism. Peroxisomal disorders include:

- Zellweger syndrome (abnormal facial features, enlarged liver, and nerve damage in infants)
- Adrenoleukodystrophy (symptoms of nerve damage can develop in childhood or early adulthood depending on the form.)

Metal metabolism disorders: Levels of trace metals in the blood are controlled by special proteins. Inherited metabolic disorders can result in protein malfunction and toxic accumulation of metal in the body:

- Wilson disease (toxic copper levels accumulate in the liver , brain, and other organs)
- Hemochromatosis (the intestines absorb excessive iron, which builds up in the liver, pancreas, joints, and heart , causing damage)

Organic acidemias: methylmalonic acidemia and propionic acidemia.

Urea cycle disorders: ornithine transcarbamylase deficiency and citrullinemia

Symptoms of Inherited Metabolic Disorders

The symptoms of genetic metabolic disorders vary widely depending on the metabolism problem present. Some symptoms of inherited metabolic disorders include:

- Lethargy
- Poor appetite
- Abdominal pain
- Vomiting

- Weight loss
- Jaundice
- Failure to gain weight or grow
- Developmental delay
- Seizures
- Coma
- Abnormal odor of urine, breath, sweat, or saliva

The symptoms may come on suddenly or progress slowly. Symptoms may be brought on by foods, medications, dehydration, minor illnesses, or other factors. Symptoms appear within a few weeks after birth in many conditions. Other inherited metabolic disorders may take years for symptoms to develop.

Diagnosis of Inherited Metabolic Disorders

Inherited metabolic disorders are present at birth, and some are detected by routine screening. All 50 states screen newborns for phenylketonuria (PKU). Most states also test newborns for galactosemia. However, no state tests babies for all known inherited metabolic disorders.

Improved testing technology is leading many states to expand newborn screening for genetic metabolic disorders. The National Newborn Screening and Genetics Resources Center provides information on each state's screening practices.

If an inherited metabolic disorder is not detected at birth, it is often not diagnosed until symptoms appear. Once symptoms develop, specific blood or DNA tests are available to diagnose most genetic metabolic disorders. Referral to a specialized center (usually at a university) increases the chances of a correct diagnosis.

Treatment of Inherited Metabolic Disorders

Limited treatments are available for inherited metabolic disorders. The essential genetic defect causing the condition can't be corrected with current technology. Instead, treatments try to work around the problem with metabolism.

Treatments for genetic metabolic disorders follow a few general principles:

- Reduce or eliminate intake of any food or drug that can't be metabolized properly.
- Replace the enzyme or other chemical that is missing or inactive, to restore metabolism to as close to normal as possible.
- Remove toxic products of metabolism that accumulate due to the metabolic disorder.

Treatment may include such measures as:

- Special diets that eliminate certain nutrients
- Taking enzyme replacements, or other supplements that support metabolism
- Treating the blood with chemicals to detoxify dangerous metabolic by-products

Whenever possible, a person with an inherited metabolic disorder should receive care at a medical center with experience with these rare conditions.

Children and adults with inherited metabolic disorders can become quite ill, requiring hospitalization and sometimes life support. Treatment during these episodes focuses on emergency care and improving organ function.