

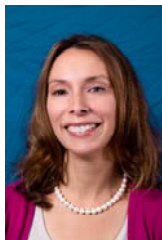
Inborn Errors of Metabolism: A Snapshot

SUMMARY

Inborn errors of metabolism (IEM) are single gene defects that result in abnormalities in the synthesis or catabolism of proteins, carbohydrates or fats. Individually they are rare but together they are common with a collective incidence in ~ 1 in 3,000 live births. Nearly every IEM has several forms that vary in age of onset, clinical severity and mode of inheritance. IEMs represent one of the few genetic diseases where prompt recognition and treatment can significantly improve outcome and morbidity/mortality.

SCIENTIST BIOGRAPHY

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INTRODUCTION

Many hereditary biochemical disorders, called inborn errors of metabolism (IEM) or inherited metabolic disorders (IMD), have been discovered over the past 50 years. Approximately 3,000 inborn errors of metabolism are known, and although individually they are rare, collectively the incidence is estimated to be greater than 1 in 3,500 live births. Inherited metabolic disorders may affect the function of any tissue in the body and may present at any age - from infancy to adulthood.

HISTORY

Normal metabolism includes all biochemical reactions within the cells of living organisms. These enzyme-catalyzed reactions allow organisms to stay alive and in a state of health. In 1902, Sir Archibald E. Garrod first introduced the concept of IEM.¹ He suggested that a block in the metabolic process that caused the disease led to the accumulation of intermediary metabolites that could not be processed further. Garrod published his findings in 1908² and is considered the "grandfather" of biochemical genetics where his discovery of intermediary metabolites from IEMs led to the discovery of enzyme defects causing these diseases. Advances in the field of genetics have come a long way since then with Johannsen introducing the concept of the gene as the unit of inheritance,³ and Pauling and Ingram conceiving the molecular disease concept.^{4,5} The understanding that deoxyribonucleic acid (DNA) was the basis of inheritance with the double helix discovered by Watson and Crick helped bring in a new era of molecular genetics.⁶ Improved methods of diagnosis and continued discoveries of gene defects have led to the discovery of IEMs that are summarized in the volumes of texts of general genetics, biochemical genetics, and neurological diseases.⁷ Many of these IEMs are treatable by nutrition management, however, for many IMDs early detection is very important so that treatment can begin before damage may occur.

NEWBORN SCREENING

Newborn screening (NBS) is a health program aimed at the early identification of conditions for which early and timely intervention can prevent or reduce associated mortality and morbidity.⁸

In 1934, Dr. Asbjorn Folling of Norway first described a condition he observed in some of his mentally handicapped patients. They had a particular odor and phenylpyruvic acid was found in their urine. He discovered that they had a deficiency in the enzyme that converts phenylalanine (PHE) to tyrosine (TYR). When this reaction does not occur, phenylalanine accumulates in the blood. High levels of phenylalanine are toxic to the developing brain of an infant and cause mental retardation. The condition was called phenylketonuria or PKU.

The next major advance in the treatment of PKU and the start of newborn screening was in the early 1960's, when Robert Guthrie developed a test that allowed presymptomatic screening of all newborns.⁹ In his work, Guthrie found that a blood spot from a heel prick placed on filter paper in a bacterial inhibition assay for PHE could be used to "screen" people for PKU. In 1962, the United States (US) Children's Bureau supported a pilot study using Guthrie's technique. In 1963, Massachusetts became the first state to mandate PKU screening for all newborns. By 1973, there were 34 states mandating PKU screening. With the launch of newborn screening, Guthrie and other researchers continued the advancement of NBS by developing other assays for other IEMs. The bacterial inhibition assay was followed by flurometric assay, enzymatic analysis, radio-labeled assays, DNA-based analysis, and mass spectrometry. Mass spectrometry (MS/MS) was introduced in the 1990s.¹⁰

MS/MS is used for NBS because it requires a very small sample size, demonstrates accuracy and precision, requires approximately 2 min per sample, can test for multiple (pre-selected) analytes without extensive prior separation or purification, and permits screening for multiple very rare disorders, using a single sample and single analysis. Now all states in the US must screen for at least 21 disorders by law, and some states screen for 30 or more.

In order for conditions to be included on the NBS panel they must meet certain criteria:

1. The condition has to manifest early
2. Biochemically and clinically definable
3. Have proven early interventions that are accessible to all newborns
4. There are interventions that can decrease morbidity/mortality
5. Have a reasonable incidence
6. Can be confirmed with tests beyond screening
7. Can be changed when evidence supports addition or elimination from the panel

In the past decade, MS/MS has been implemented in the NBS programs around the world. The incidence of disorders detected through NBS has been calculated to be approximately 1 in every 3,000 newborns screened.¹⁰

PATTERNS OF INHERITANCE

There are three patterns of inheritance that are most common in IEM: autosomal recessive, autosomal dominant, and X-linked. Common IEMs are usually single gene-defects, inherited in an autosomal recessive fashion. Autosomal recessive means that the defects are on other chromosomes than the sex chromosome. The mother and father both have to be carriers of the defective gene. These altered genes are inherited from both mother and father just like other features such as eye and skin color. Genetic information, which determines each person's characteristics, is carried on pairs of genes in every body cell. These genes serve as blueprints, or patterns.

Each parent of a child with an IEM has one normal (□) and one altered IEM (■) gene. Each one of their offspring could have one of four gene sets (Figure 1).

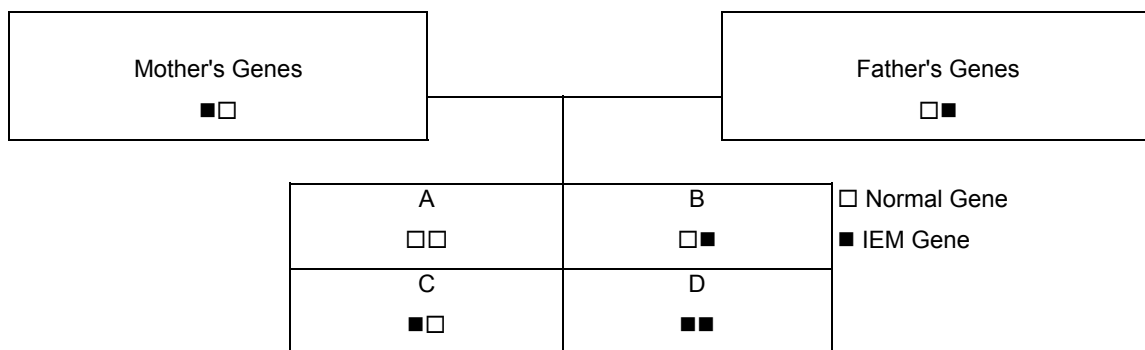


Figure 1. Autosomal Recessive inheritance of IEM

A child who receives gene set A inherits two normal genes (□□). Her body will make enough enzyme for the metabolic pathway to function normally. She will pass a normal gene on to each of her offspring.

A child who receives gene set B or C inherits one normal (□) and one IEM (■) gene. His body will make enough enzyme for the metabolic pathway to function normally, but can pass on the IEM gene to his/her offspring. A person with this gene set - 1 normal and one IEM- is called a *carrier*. Being a carrier generally does not affect the person's health. Parents of a child with an IEM are carriers. Brothers and sisters of a child with an IEM may be carriers too.

A child with gene set D has an IEM caused by the two IEM genes (■■), one from the mother and one from the father. Her body will not be able to process certain metabolic pathways normally. She will also pass an IEM gene on to each of her offspring.

In autosomal dominant inheritance, only one copy of the mutated gene is needed to inherit the disorder.⁷ It can come from the mother or the father, therefore there is a 50% chance of the child being affected with an IEM. Unaffected siblings would not carry the defective gene as is possible in an autosomal recessive inheritance. Dominant mutations can also occur spontaneously with neither parent being a carrier.

X-linked recessive disorders occur due to mutations of genes on the X sex chromosome. Males have one X and one Y chromosome and women have two X chromosomes. Women will be carriers of the defective gene only and men will be affected by the gene, meaning they will have an IEM.

SIGNS AND SYMPTOMS

An IEM can present at any age from birth through adulthood. An IEM should be suspected whenever a newborn infant has acute metabolic decompensation after a period of normal behavior and feeding. It should also be thought of when a person of any age presents with unexplained lethargy/coma, recurrent seizures, failure to thrive, persistent vomiting, jaundice, unusual body odor, developmental delay hyperammonemia, hypoglycemia, metabolic acidosis, or a family history of unexplained deaths in siblings/family members. If an IEM is suspected, a metabolic specialist should be consulted for an appropriate course of action.

INHERITED METABOLIC DISORDERS

Once the diagnosis of an IEM has been made, therapy will then be tailored to the specific disorder. There are metabolic disorders of amino acid, carbohydrate, and fatty acid metabolism.

AMINO ACID METABOLISM DISORDERS

A disorder of amino acid metabolism occurs when there is reduced activity or absence of a specific enzyme or cofactor. If a person is not treated, then the amino acids and breakdown by-products build up in the blood and tissues and may spill into the urine and perspiration. The buildup of these toxic metabolites is what causes the signs and symptoms of the disorder. If not treated, irreversible brain or neurologic damage and possibly death may occur. For example, in PKU a person may not have enough working phenylalanine hydroxylase, an enzyme that converts PHE to TYR. If a person has PKU and is ingesting protein, PHE will not be converted to TYR and PHE and its by products will build up in the brain and tissues resulting in the symptoms of PKU. If left untreated, permanent brain damage can occur.

These IEMs are typically disorders of essential amino acids (EAA). This means that the body has to ingest these EAAs in order to grow and develop, however in someone with this type of IEM, only a small amount can be tolerated; excess may cause harm. Types of amino acid disorders include: hyperphenylalaninemias, tyrosinemias, maple syrup urine disease, homocystinuria, urea cycle disorders, and organic acidemias. Together they make up approximately 20 different disorders of amino acid metabolism all with varying levels of severity.

Nutrition management for these IEMs is mainly through substrate restriction which involves limiting one or more essential amino acids while providing adequate amounts of energy and nutrients to promote normal growth and development. However, management may also include supplementing the end product, supplementing the enzyme cofactor or a combination of all or any of these approaches. Amino acid requirements are individualized and careful and frequent monitoring is required to ensure the adequacy of the nutritional prescription.¹¹

FATTY ACID OXIDATION DISORDERS

Fatty acid oxidation disorders (FAODs) are a family of at least 22 different inherited genetic disorders in the mitochondrial fatty acid oxidation pathway.¹² Similar to amino acid metabolism disorders, FAODs have not enough or no working enzyme to complete a metabolic pathway. Severity can range from mild to severe depending upon the amount of enzyme present. FAODs can have a defect in short-chain, medium-chain, long-chain, or very-long chain fatty acid metabolism. Symptoms are often induced by fasting or an infection with vomiting and/or diarrhea. Lethargy, muscle weakness, and seizures may occur. More severe symptoms include hepatic encephalopathy, progressing to coma and often death¹³, as well as cardiomyopathy that is a frequent life-threatening complication in acute metabolic decompensation.¹² Another common biochemical sign in those with FAODs is an abnormal response to fasting that is characterized by low ketone production paired with increased energy demands. The consequence is fasting hypoglycemia often paired with severe acidosis.

Nutrition management includes the avoidance of fasting, typically no longer than 4 hours in infants and no longer than 8 hours in children. Adults may be able to fast for 10 hours. Some may need continuous nighttime feedings or cornstarch to help maintain blood glucose levels. Cornstarch is chosen because it is a complex carbohydrate that is slowly digested for gradual glucose release. Fat restriction (or alteration in the type of fat ingested) is recommended and high carbohydrate intake for energy is also needed. The goal is to prevent body fat breakdown so the caloric



intake must meet demand for stress, illness, and exercise. Possible supplementation with Medium Chain Triglycerides (MCT) oil or carnitine may also be needed depending on the FAOD.

CARBOHYDRATE METABOLISM DISORDERS

Carbohydrate disorders may result from deficiencies of enzymes that split sugars to their smallest parts in the small intestine or from a deficiency of a compound that carries glucose and galactose from the small intestine into the blood. Symptoms of carbohydrate disorders may be similar, whatever the cause, and include watery diarrhea, gas, and bloating. Abdominal cramping may occur and if diarrhea persists, dehydration and acidosis may be severe. There can be organ involvement, such as the liver, where certain enzyme activity and metabolic pathways are centered. Treatment is mainly nutrition management which involves substrate restriction such as lactose/galactose restriction in someone with galactosemia.

In addition to disorders involved in the breakdown of carbohydrates, there are several different inherited enzyme defects that interfere with the breakdown of glycogen (a storage form of carbohydrate in the body) and raise the glycogen content of the organ in which the enzyme is located. Because stored glycogen is a between-meal and nighttime source of blood sugar, when enzymes that breakdown glycogen do not function, blood glucose concentrations often drop to dangerously low levels. Nutrition management includes maintaining normoglycemia by providing a continuous glucose supply. It may also be necessary to restrict carbohydrates in the pathway such as lactose and fructose, as well as limiting fat intake.

There can also be enzyme defects in the glucose transport protein (GLUT1) found in erythrocytes, fibroblasts, and the blood-brain barrier. GLUT1 functions effectively in glucose uptake in the absence of insulin. Clinical features include seizures, delayed mental and motor development, hypotonia, and impaired language skills and behavior. Consequently when this enzyme is deficient, the body must use fat as a fuel source. The ketogenic diet is commonly used as nutrition management. The ketogenic diet is a rigid, mathematically calculated, doctor-supervised therapy.¹⁴ It is high in fat and low in carbohydrate with adequate protein, providing 3-5 times as much fat as carbohydrate and protein combined. This combination changes the way energy is used in the body. Fat is converted in the liver into fatty acids and ketone bodies. This elevated level of ketone bodies in the blood (ketosis) leads to a reduction in the occurrence of seizures.

NUTRITION MANAGEMENT OF IEM

The goal of treatment is to maximize the individual's potential by avoiding symptoms at reasonable "cost" by biochemical manipulation through diet, drugs, or other therapies based on the specific disorder. Due to the nature of these disorders, nutritional management is the mainstay of treatment. Medical foods have been developed for the nutritional management for many disorders. The nutrient composition of these medical foods are based on clinical research findings and recognized nutrient needs for growth and maintenance of nutrition status of infants, toddlers, children and adults. These medical foods are complete foods except for the removal or modification of disease-specific nutrients.

Manipulation of precursors and limitation of substrates that lead to toxic metabolites form a major portion of the available therapies for many IEMs.¹⁵ The goals of nutrition support include: enhancing anabolism and depressing catabolism, correcting the primary imbalance in the metabolic pathway, providing alternative metabolic pathways, supplementing product of the blocked primary pathway, supplementing "conditionally" essential nutrients, and stabilizing the altered enzyme protein.¹⁶



CONCLUSION

Most IEMs are single gene defects that result in abnormalities in the synthesis or catabolism of proteins, carbohydrates or fats. Most are due to a defect in an enzyme or transport protein causing a block in a metabolic pathway. The effects are due to toxic accumulations of substrates before the block. Individually they are rare but together they are common with a collective incidence in ~ 1 in 3,000 live births. Nearly every IEM has several forms that vary in age of onset, clinical severity and mode of inheritance. Failure to adapt nutrient intake to individual needs of each patient can result in mental retardation, neurologic crisis, growth failure, and possibly death. IEMs represent one of the few genetic diseases where prompt recognition and treatment can significantly improve outcome and morbidity/mortality. Treatment requires an accurate diagnosis, early intervention, and knowledge of the pathogenesis of the disorder. Early identification of selected inborn errors will lead to a significant reduction in morbidity, mortality, and associated disabilities in affected individuals. Nutrition therapy, including the use of medical foods, is frequently the only treatment available. Proper nutrition management is essential in these disorders amendable to diet treatment and may prevent mental handicap and, possibly, death. Nutrition therapy for these individuals is for life.

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