Clinical Approach to the Diagnoses of Inborn Errors of Metabolism

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KEYWORDS

- Inborn errors of metabolism • Developmental delay
- Replacement therapy • Newborn screening • Phenylketonuria
- Fatty acid oxidation disorders

Inborn errors of metabolism (IEMs) are a set of relatively uncommon complicated medical conditions involving abnormalities in the complex biochemical and metabolic pathways of the human body system. They involve great complexity of the underlying pathophysiology, biochemical workup, and analysis, and have complicated therapeutic options for management. These children are often sick with significant complications and high rates of morbidity and mortality. The understanding of these complex disorders requires special in-depth training and experience. Most primary care physicians are less familiar with these disease conditions, and therefore less willing to deal with them because of the complexity involved. There are metabolic specialists available, mostly in large medical centers, with expertise to deal with these intricate complicated issues. Primary care physicians and pediatricians usually are the first point of contact for most of these newborns, children, or adolescents, however. Therefore, it is important that primary care physicians become comfortable in being able to recognize early signs and symptoms, be able to initiate appropriate diagnostic and therapeutic interventions, and be able to make appropriate referrals.

The following article summarizes the key issues basic to understanding IEMs. The main points of discussion address the following questions:

What are IEMs?
What are the different types of IEMs?
What is the relative frequency of these IEMs?
What is the inheritance pattern of these IEMs?
How can these IEMs be diagnosed in a timely manner?
What is the role of newborn screening (NS) programs in early diagnosis and prevention of morbidity and mortality?

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What are the treatment and management options for these IEMs?
What is the long-term prognosis for patients who have IEMs?

WHAT ARE INBORN ERRORS OF METABOLISM?

The term *metabolism* encompasses the net result of a multitude of complex biochemical processes that occur in living organisms to maintain cellular activities. These processes are organized into specific metabolic pathways with the primary function to maintain daily life activities. Each pathway depends on certain substrates and specific enzymes to ensure smooth functioning. IEMs are a group of heritable genetic disorders interfering with these metabolic pathways in different ways, leading to inadequate functioning of a particular pathway. This interference in the normal enzymatic or metabolic pathway has varying consequences, including deficiency of a particular end product or excessive accumulation of a substrate that may be toxic. Either of these two scenarios leads to significant morbidity and mortality by hampering normal functioning of a particular metabolic pathway.

IEMs have been known for the approximately the past 100 years, with the term being first used by Sir Archibald Garrod in 1902.[1] The initial disorders described were alkaptonuria, benign pentosuria, albinism, and cystinuria at that time, to be followed by description of one of the major IEMs, namely, phenylketonuria (PKU), by Folling in 1934. Since that time, advances in medicine have uncovered more than 500 IEMs.[2]

WHAT ARE THE DIFFERENT TYPES OF INBORN ERRORS OF METABOLISM?

Some of the common metabolic disorders are listed in **Box 1**.[3,4]

WHAT IS THE RELATIVE FREQUENCY OF OCCURRENCE OF INBORN ERRORS OF METABOLISM?

The incidence of IEMs is highly variable among the many specific clinical entities, ranging from 1 in 400 US African Americans for hemoglobinopathies, 1 in 4500 for congenital hypothyroidism, 1 in 15,000 for PKU, to 1 in 100,000 for most of the fatty acid disorders (except MCAD) and organic acidemias. Incidences of some common inborn errors are listed in **Table 1**.[3]

WHAT IS THE INHERITANCE PATTERN OF INBORN ERRORS OF METABOLISM?

Several patterns of inheritance are possible for the different IEMs. It is important to detail a three- to four-generation pedigree to evaluate the mode of inheritance accurately.

Autosomal recessive (AR) inheritance is the most common mode of inheritance for metabolic disorders. In this case, both the parents are heterozygous for the mutant gene; hence, they do not express the disorder, but the offspring are homozygous for that particular gene defect; hence, they express the defect and present clinically with the disorder. The family history is generally negative in the parents, but there may be a history of early neonatal deaths or a clinical disorder expressed as a concern. Consanguinity has an increased chance of expression of an AR disorder. Rarely, these mutations may occur de novo.[5]

X-linked recessive inheritance may also be seen in some IEMs, in which one copy of the mutated gene on the X-chromosome is sufficient for causing the disorder. Therefore, in this mode of inheritance, the disorder is transmitted from a carrier mother to her male offspring. Also, de novo mutations are observed with a much higher incidence in this pattern of inheritance.[5]

Autosomal dominant (AD) inheritance is a less common mode of inheritance for IEMs. The incidence of de novo mutations causing AD disorders is much higher than in other patterns of inheritance. AD transmission generally means that one of