Inborn Errors of Metabolism and Other Genetic Disorders

Inborn errors of metabolism are well-characterized genetic abnormalities that give rise to metabolic disorders. Since Sir Archibald Garrod coined the term in 1908, the number of such diseases that have been recognized has increased exponentially and a comprehensive discussion of these diseases is beyond the scope of this chapter. *Most inborn errors of metabolism are rare diseases that are generally inherited as autosomal recessive or X-linked traits* (Chapter 5). Mitochondrial disorders (Chapter 5) form a distinct entity by themselves. Some of the clinical features that suggest an underlying metabolic disorder in a neonate are listed in Table 10-4. Three genetic disorders of metabolism, phenylketonuria (PKU), galactosemia, and cystic fibrosis, are selected for discussion here. PKU and galactosemia are reviewed because their early diagnosis (via neonatal screening programs) is particularly important and with appropriate dietary regimens early death or mental retardation can be prevented. Cystic fibrosis is included because it is one of the most common, potentially lethal diseases occurring in individuals of Caucasian descent.

Phenylketonuria

There are several variants of this inborn error of metabolism, which affects 1 in 10,000 live-born Caucasian infants. The most common form, referred to as *classic phenylketonuria*, is quite common in persons of Scandinavian descent and is distinctly uncommon in African American and Jewish populations.

Table 10-4 Abnormalities Suggesting Inborn Errors of Metabolism

General
Dysmorphic features
Deafness
Self-mutilation
Abnormal hair
Abnormal body or urine odor ("sweaty feet"; "mousy or musty"; "maple syrup")
Hepatosplenomegaly; cardiomegaly
Hydrops
Neurologic
Hypotonia or hypertonia
Coma
Persistent lethargy
Seizures
Gastrointestinal
Poor feeding
Recurrent vomiting
Jaundice
Eyes
Cataract
Cherry red macula
Dislocated lens
Glaucoma
Muscle, Joints
Myopathy
Abnormal mobility

Adapted from Barness LA, Gilbert-Barness E: Metabolic diseases. In Gilbert-Barness E, et al (eds): Potter's Pathology of the Fetus, Infant, and Child. St. Louis, Mosby, 2007.

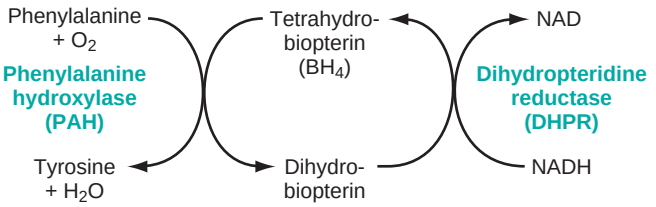

Figure 10-14 The phenylalanine hydroxylase system. Deficiency of PAH and DHPR can give rise to phenylketonuria.

Phenylketonuria (PKU) is an autosomal recessive disorder caused by a severe deficiency of the enzyme phenylalanine hydroxylase (PAH) and the resultant hyperphenylalaninemia. Affected infants are normal at birth but within a few weeks develop a rising plasma phenylalanine level, which impairs brain development. Usually by 6 months of life *severe mental retardation* becomes evident; fewer than 4% of untreated phenylketonuric children have IQs greater than 50 or 60. About one third of these children are never able to walk, and two thirds cannot talk. *Seizures,* other neurologic abnormalities, *decreased pigmentation of hair and skin,* and *eczema* often accompany the *mental retardation* in untreated children. Hyperphenylalaninemia and the resultant mental retardation can be avoided by restricting phenylalanine intake early in life. Hence, several screening procedures are routinely performed to detect PKU in the immediate postnatal period.

Many female PKU patients, if treated with dietary restriction early in life, reach childbearing age and are clinically asymptomatic. Most of them have marked hyperphenylalaninemia, because dietary treatment is discontinued after they reach adulthood. Between 75% and 90% of children born to such women are mentally retarded and microcephalic, and 15% have congenital heart disease, even though the infants themselves are heterozygotes. This syndrome, termed *maternal PKU*, results from the teratogenic effects of phenylalanine or its metabolites that cross the placenta and affect specific fetal organs during development. The presence and severity of the fetal anomalies directly correlate with the maternal phenylalanine level, so *it is imperative that maternal dietary restriction of phenylalanine be initiated before conception and continued throughout pregnancy*.

The biochemical abnormality in PKU is an inability to convert phenylalanine into tyrosine. In normal children, less than 50% of the dietary intake of phenylalanine is necessary for protein synthesis. The remainder is converted to tyrosine by the phenylalanine hydroxylase system (Fig. 10-14). When phenylalanine metabolism is blocked because of a lack of PAH enzyme, minor shunt pathways come into play, yielding several intermediates that are excreted in large amounts in the urine and in the sweat. These impart a *strong musty or mousy odor* to affected infants. It is believed that excess phenylalanine or its metabolites contribute to the brain damage in PKU. Concomitant lack of tyrosine (Fig. 10-14), a precursor of melanin, is responsible for the light color of hair and skin.

At the molecular level, approximately 500 mutant alleles of the *PAH* gene have been identified, only some of which cause a severe deficiency of the enzyme and thus result in classic PKU. Infants with mutations resulting in a complete lack of PAH activity present with the classic features of PKU, while those with up to 6% residual activity present