

Disorders Currently Detectable by Newborn Screening

Introduction

As noted in chapter 5, the identification of phenylketonuria (PKU) and discovery of the treatment to prevent its associated mental retardation provided the first major impetus for routine newborn screening. The clinical course and characteristics of PKU and the following eight congenital disorders detectable through newborn screening are described below:

1. congenital hypothyroidism,
2. galactosemia,
3. maple syrup urine disease (MSUD),
4. homocystinuria,
5. biotinidase deficiency,
6. sickle cell anemia,
7. cystic fibrosis, and
8. congenital adrenal hyperplasia (CAH).

These disorders (with the exception of most cases of congenital hypothyroidism) are genetic in origin and are transmitted in a recessive genetic pattern. They are amenable to newborn screening techniques because of quantitative or qualitative differences detectable in certain biochemical markers. As outlined below, some of the disorders are treatable by supplying the missing enzyme or end product or by removing substances from the child's environment.

Phenylketonuria

The group of disorders that are included under the heading of PKU share a common feature: impaired metabolism of phenylalanine, an amino acid contained in protein. This genetic abnormality prevents the normal conversion of phenylalanine into tyrosine, a reaction occurring in the liver (454). Defects in the production of certain enzymes result in the progressive accumulation of phenylalanine in the blood and tissues. The abnormally high levels of this amino acid in the blood and tissues interfere with brain development and cause damage to the central nervous system, although the mechanism by which this damage occurs is not known (597).

Newborn infants with PKU appear normal at birth and, because of the disease, frequently go on to develop excessively blond hair, blue eyes, and fair skin. Various manifestations of the disorder begin to appear in the first few months of life, including irritability,

diaper rash, seizures, and delayed development. Gradually, it becomes apparent that the infant is obviously mentally retarded. It is estimated that **96 to 98** percent of all untreated infants with classical PKU will become mentally retarded, most of them severely or profoundly retarded (644).¹ With supportive care alone, the disease is not directly lethal, but the overall lifespan of mentally retarded individuals with PKU is reduced. The incidence of classical PKU is usually between 1 in 10,000 and 1 in 15,000 live births (378), although in some populations it is even rarer (e. g., PKU is particularly rare in blacks).

Treatment consists of restriction of dietary phenylalanine to the minimum amount required for growth and development. A special formula for newborns and a food substitute for older children that restricts intake of phenylalanine from the diet is necessary to provide a nutritionally adequate diet when natural protein sources are restricted. If the special diet is begun before 2 to 4 weeks of age and maintained properly throughout development (and possibly indefinitely), infants with PKU can attain normal development, behavior, and intelligence. Such treatment generally does not reverse mental retardation if started well after symptoms have appeared. However, recent evidence suggests that some perceptual motor problems and learning disabilities may exist even in treated children with PKU, and it is not yet known whether these can be completely avoided (485). The average lifespan of treated individuals is unknown, but it is expected to be unaffected by PKU. Periodic monitoring of blood phenylalanine levels is needed to ensure that the level is within safe limits during development, and a nutritionist usually assists in monitoring and coordinating nutritional regimens. Current recommendations are that the special diet be continued indefinitely. The need for dietary restriction in individuals with PKU beyond adolescence has not been investigated.

For many years, it has been known that excess phenylalanine in a mother acts as a teratogen to the fetus: high maternal blood phenylalanine levels (above

¹PKU a condition characterized by the progressive accumulation of phenylalanine in the blood and tissues (hyperphenylalaninemia), exists not only in its classical form, which is associated with severe mental retardation, but also in a spectrum of milder forms, in which developmental delay is more variable. Some of the milder forms do not result in mental retardation and do not require treatment.

20 mg/dl) during pregnancy are associated with a high rate of mental retardation, microcephaly, congenital heart defects, and low birthweight among offspring of women with untreated maternal PKU (346,392). Maintaining normal phenylalanine levels by dietary restriction in mothers with PKU can be successful in preventing at least some of these adverse effects in offspring (371), but treatment of women with PKU after a pregnancy has begun appears to be ineffective or only partially effective.

The overall efficacy of a phenylalanine-restricted diet during pregnancy in preventing the complications of maternal PKU is currently being examined by a U.S. and Canadian prospective collaborative study funded by the National Institute of Child Health and Human Development (346). As many as possible of the estimated 2,400 women in the United States at risk for maternal PKU are being followed and advised to go on the special diet before and during pregnancy. After the study is complete, the responsibility for tracking women with PKU during their childbearing years will fall on the individual screening programs. This tracking will require reliable monitoring systems and thorough educational efforts to maintain contact with women at risk.

Congenital Hypothyroidism

Infants with congenital hypothyroidism have a deficiency of thyroxine (T₄), a hormone essential for physical growth and early brain development. Without thyroxine, permanent, irreparable brain damage occurs. The thyroid gland may be missing, incompletely developed, dislocated, or dysfunctional in congenital hypothyroidism (551), and each form of the disease may be associated with a different cause. Accordingly, symptoms vary widely among children with congenital hypothyroidism, and the prognosis may vary from case to case (360). In all of them, however, the infants' thyroid glands are unable to produce sufficient thyroxine, whether or not there are high serum levels of thyroid-stimulating hormone.

Congenital hypothyroidism is several times more frequent than PKU, with an incidence rate estimated at 1 in 3,000 to 1 in 4,000 live births. It is one of the more common causes of mental retardation, and is more common in girls than in boys. It is not considered to be genetic in origin in more than about 25 percent of cases. Most infants with congenital hypothyroidism lack conspicuous features of the disease in the first few days after birth. Later on, constipation, lethargy, prolonged jaundice, poor feeding, and hypothermia are among the nonspecific neonatal symptoms that commonly develop (360). The progressive course

of the disease eventually results in mottled dry skin, coarse facial features, growth retardation, and impaired motor function. Most critically, the disease interferes with brain function and normal growth and development, and leads to some degree of mental retardation. Before screening for congenital hypothyroidism was available, most infants with the disease were diagnosed on the basis of some of these symptoms sometime after 3 months of age or even much later. By that time, however, irreversible damage to the brain had usually occurred.

Treatment for congenital hypothyroidism depends on daily oral ingestion of tablets containing L-thyroxine to raise serum thyroxine levels into the normal range. The tablets should be taken indefinitely, and serum thyroxine levels should be monitored periodically to prevent overtreatment or undertreatment. Treated children appear to be normal in intellectual, psychosocial, and physical development. Recent observations have suggested, however, that there may be some residual behavioral problems; subtle, minor differences have been noted between some treated children and their normal siblings (550). The severity of the children's condition at birth and the time it took to bring their serum thyroxine levels into the normal range may account for these findings, but systematic, long-term followup is needed to determine final outcome. There is general agreement that screening and early treatment are essential to improved outcome in patients with this disorder.

Galactosemia

The initial symptoms of galactosemia occur in the first week of an infant's life, with vomiting after the start of milk ingestion. Increasing lethargy and liver dysfunction may occur soon thereafter, and unless treated immediately, galactosemia can be rapidly fatal. Septicemia (blood poisoning) and progressive liver damage are the most common causes of death in infants with untreated galactosemia. Mental retardation, cataracts, and cirrhosis of the liver are the most frequent consequences of suboptimal treatment in the survivors who are eventually diagnosed on the basis of clinical presentations. The average age at diagnosis of these infants is 3 to 6 weeks.

The symptoms of galactosemia result from an accumulation of galactose (a component of the sugar (lactose) found in milk) and a metabolite known as galactose-1-phosphate in the blood, leading to excretion of high levels of galactose in the urine. Galactose, absorbed in the small intestine from milk and milk products, is normally converted to glucose in the liver. Infants with galactosemia are deficient in one of the

enzymes that is required to catalyze this reaction, so galactose and products of its metabolism accumulate unmetabolized. The disorder is found in approximately 1 in **60,000** live births. Screening for galactosemia using cord blood would be even better than using newborn blood in facilitating the earlier diagnosis and initiation of treatment.

To avert neonatal death or mental retardation, screening for galactosemia must be done in the first few days of life. Treatment for galactosemia depends on completely eliminating milk and its products from the diet throughout an individual's life. Overall, the elimination of milk products prevents early death and promotes normal mental and physical development in most children with galactosemia, and long-term studies show normal adult functioning in most early treated cases (138).

The results of apparently optimal treatment for galactosemia have not been completely satisfactory in all cases, as a small percentage of treated children have had major neurological deficits (546). Many girls with galactosemia seem to have developed ovarian failure despite treatment. Finally, a specific speech abnormality (verbal dyspraxia) is being reported in an increasing number of individuals with galactosemia, despite their having received the same treatment that prevented such symptoms in other individuals (**82,735**).

Maple Syrup Urine Disease

MSUD (also called branched-chain ketoaciduria) is a disorder of amino acid metabolism involving the three branched-chain amino acids: leucine, isoleucine, and valine. Affected individuals have a deficiency of one of the enzymes that control the pathway of the catabolism of these amino acids. Several forms of MSUD have been reported: a classic, severe form and milder variant forms. The urine of affected individuals has a distinctive odor that has been described as smelling like maple syrup. The incidence of classic MSUD **ranges from 1 in 120,000 to 1 in 290,000**, with a figure of 1 in 225,000 being most frequently cited (455).

Infants with MSUD appear normal at birth, but by the end of the first week, develop worsening signs of central nervous system damage with poor feeding and vomiting. Convulsions and lethargy leading to coma may occur shortly thereafter. The infants become progressively more lethargic and may suddenly go into a coma and die from profound ketoacidosis and brain damage, not uncommonly in the first 2 weeks of life (**633**). **Electroencephalographic abnormalities** support the evidence of severe brain dysfunction in infants with MSUD. Few manage to survive untreated, although

they usually sustain severe mental and motor retardation (**453**).

Newborn screening for this disorder is useful only if it leads to rapid diagnosis and immediate treatment in the first week or two of life. Treatment must be life-long and consists of dietary restriction of the branched-chain amino acids. As in treatment for PKU, a special formula is necessary to ensure adequate nutrition. Initiation of the special diet before the onset of acute symptoms can result in survival with normal intelligence, although the long-term prognosis of treated children with MSUD is still unknown.

Homocystinuria

Classical homocystinuria is caused by a deficiency of one of the enzymes involved in the metabolism of an amino acid known as homocystine. As a result of this enzyme deficiency, homocystine and another amino acid, methionine, accumulate in the body and are excreted in large amounts in the urine.²

The incidence of classical homocystinuria has been estimated at 1 in 200,000 live births (437), but this figure may be an underestimate since it is based on the number of cases detected through newborn screening performed in the first week of life, and screening at this time may miss as many as **50 percent** of affected cases. The optimal time for collecting blood for newborn screening for this disorder is 4 to 6 weeks of age (453).

An infant born with homocystinuria develops clinical signs of the disease relatively slowly. Developmental retardation is the first general sign of the disease. A number of manifestations may appear during childhood or later in life—e.g., downward dislocation of the ocular lenses; thinning and lengthening of the long bones; sparse, fair hair; and seizures. Homocystinuria can lead to life-threatening episodes of vascular thrombosis (clotting of blood). It has been estimated that most of the surviving, untreated infants with this disease go on to have mental deficiency, and half of them may die by age **25**.

The major mental and motor manifestations of homocystinuria may be controlled if affected infants who are not biochemically responsive to vitamin B₆ are treated with a diet that restricts dietary intake of methionine and those who are vitamin B₆ responsive are treated with vitamin B₆. Long-term prognosis of those who are treated, particularly the risk of thrombosis, is not known.

²Classical homocystinuria, in which there is an increased methionine level, can be detected by current tests used in newborn screening. There are other forms, however, that do not have an increased methionine level and cannot be detected by these tests.

Biotinidase Deficiency

The cause of biotinidase deficiency is an inability to recycle the B vitamin biotin. The incidence of this disorder has been estimated at 1 in 45,000 live births (759). Infants with biotinidase deficiency appear normal at birth, but may develop symptoms of the disorder in the first weeks or months of life. The most common presenting symptoms include seizures, ataxia, hypotonia, developmental delay, hearing loss, skin rash, and/or loss of hair. If untreated, biotinidase deficiency can lead to acidosis, resulting in coma or death in infancy (760).

Biotinidase deficiency is one of the most recent additions to newborn screening programs, so current experience with its diagnosis and treatment is still limited. Since symptoms can appear as early as 3 weeks of age and can be rapidly fatal, screening in the first week of life is probably the optimal time for detecting this disease. Experience to date suggests that affected infants can improve markedly with oral doses of biotin and that this treatment can prevent most or all of the symptoms of the disease. If treatment for biotinidase deficiency is begun too late, however, irreversible neurologic damage can result. Evidence suggests that this damage can occur before the onset of overt clinical signs of the disease (760).

Sickle Cell Anemia

Sickle cell anemia is caused by an abnormality in the beta globin chain of the oxygen-carrying molecule, hemoglobin, in the blood. The red blood cells become distorted in shape and have shorter useful lifespans in the circulatory system. The misshapen cells block small blood vessels, obstructing the flow of blood, leading to cell death in various organs in the body. The disease occurs in about 1 in 500 U.S. black newborns and also with relatively high frequency among people of Mediterranean and Middle Eastern descent.

The clinical course of sickle cell anemia is quite variable. Appearing normal at birth, infants with this disease may seem to be in pain and act irritable without apparent reason. Some infants with sickle cell anemia succumb to severe bacterial infections, such as septicemia, pneumonia, or meningitis in the first few years of life. When these infections occur, they can develop without overt initial symptoms or fever and may proceed rapidly, with death occurring in less than 12 hours. Overall, there may be a 10- to 20-percent mortality rate in infants with sickle cell anemia in the first year of life. **Between 6 months and 1 year of age, chronic hemolytic anemia** may begin to manifest itself, leading to long-term, debilitating complications

that affect general health, growth, and development. Painful episodes of vase-occlusive crises (i.e., obstruction of veins and arteries) are the hallmark of the disease. For the majority of infants with sickle cell anemia who survive infancy, there is wide variability in severity of the disease through childhood, adolescence, and adulthood.

There is no overall treatment or cure for sickle cell anemia. It is possible to prevent the occurrence of overwhelming infection in children with the disease by administering prophylactic penicillin beginning by 4 months of age and continuing beyond age 3. Such treatment has been shown to reduce overall morbidity and mortality from infection in affected infants (198,747). Blood transfusions may be needed at various times to increase oxygen-carrying capacity. Ongoing monitoring and treatment of acute crises may be necessary to maintain an adequate quality of life.

Newborn screening for sickle cell anemia, allowing administration of antibiotics before the disease would normally have been diagnosed, may be lifesaving for a certain percentage of infants with the disease. For others, it may allow for improved medical care by directing these infants to specialized treatment centers at an earlier time,

Cystic Fibrosis

Cystic fibrosis is a disorder of exocrine glands, characterized by thick secretions obstructing different organs, particularly the lungs, sweat glands, and pancreas. Its underlying cause is unknown, but it seems to involve a defect in chloride transport across cell membranes. It is thought to be the most common potentially fatal genetic disease in the Caucasian population, with an incidence of about 1 in 2,000 live births.

In most infants with cystic fibrosis, the disease begins its course with nonspecific symptoms. Some infants are detected at birth because of a specific form of bowel obstruction (meconium ileus). Most cases, however, manifest in infancy or early childhood with failure to thrive, diarrhea due to poor digestion and absorption of food, and persistent or recurrent signs of lung infections, which are due to thick sticky mucus in the bronchial tree.

Children with cystic fibrosis **have** no associated mental disabilities. Their overall physical problems—poor growth, intestinal malabsorption, recurrent pneumonias, and chronic respiratory disease—are progressive and disabling, however, and have social as well as medical consequences. Improvements in medical care and increased awareness of the disease have led to better survival in children with cystic fibrosis. Although death in childhood still occurs as a result of

the disease, the average lifespan of affected individuals who have been treated through normal medical channels is now above **20 years**.

Current treatment for cystic fibrosis is partially preventive and partially palliative. The inability to secrete normal amounts of digestive enzymes into the intestines (preventing the absorption of protein and fat from the diet) leads to nutritional deficiencies that can be corrected with supplemental vitamins and pancreatic replacement therapy if the disease is diagnosed sufficiently early in life. Salt supplements may be needed to counteract excessive salt loss in sweat, and antibiotics administered prophylactically can reduce incidence and effects of infections. Respiratory dysfunction eventually predominates, however, and generally determines the severity of the case. Obstructive lung disease with heart failure is the most common cause of death in individuals with cystic fibrosis, and at present, there is no cure for this problem. Whether early diagnosis and treatment will improve the long-term prognosis for patients with cystic fibrosis is still uncertain.

Congenital Adrenal Hyperplasia

The most common form of CAH, resulting from a deficiency of the enzyme 21-hydroxylase **(276) affects clinical manifestations** in infant girls more dramatically than in infant boys. The typical female patient with the disease is born with masculinization of the external genitalia and may be sent home from the hospital as a male, while the typical male infant with the disease has normal genitalia at birth. In the first week of life, a significant proportion of patients with the salt-

wasting form of CAH (about one-half of all patients with the disease) undergo a severe salt-losing crisis that is rapidly fatal if not treated immediately.

Some infant girls with CAH who survive the first few weeks of life require reconstructive surgery, but if the underlying cause of their disease is not treated, they will continue to masculinize and may go on to have short adult stature, and no breast development or menstruation. In contrast, the typical infant boy with CAH appears to develop normally in infancy, but enters puberty prematurely, resulting in short adult stature.

CAH results from a deficiency of one or another of the enzymes in the adrenal cortex that are required for normal steroid hormone synthesis. This prevents the synthesis of cortisol, leading to excessive androgen synthesis. In some forms of CAH, aldosterone production is also affected. These hormones are necessary for the body to manage stress and control salt content of tissues. The symptoms of CAH result from a deficiency of some hormones and an overproduction of others.

The prevalence of classic salt-wasting CAH ranges from approximately 1 in 11,500 to 1 in 18,250 (276, 609), but varies widely in different populations (e.g., it occurs in 1 in 3,000 live births in Alaskan Eskimos). Newborn screening can be particularly useful for detecting and treating the salt-wasting form of CAH, since infants with this form of the disease are at risk for sudden death very soon after birth if they are not properly treated. Infants with either form of the disease require replacement of missing hormones (hydrocortisone with or without mineralocorticoids) to prevent excessive androgen production and its effects on growth and reproductive functioning.