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CAUSES OF THE ORIGIN OF METABOLIC SYNDROME AND METHODS OF ITS ELIMINATION

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Annotation: Metabolic disease**,** any of the diseases or disorders that disrupt normal metabolism, the process of converting food to energy on a cellular level. Thousands of enzymes participating in numerous interdependent metabolic pathways carry out this process. Metabolic diseases affect the ability of the cell to perform critical biochemical reactions that involve the processing or transport of proteins (amino acids), carbohydrates (sugars and starches), or lipids (fatty acids).

Key words: Metabolic, acid, diagnosis,during, new technology.

Metabolic diseases are typically hereditary, yet most persons affected by them may appear healthy for days, months, or even years. The onset of symptoms usually occurs when the body's metabolism comes under stress—for example, after prolonged fasting or during a febrile illness. For some metabolic disorders, it is possible to obtain prenatal diagnostic screening. Such analysis usually is offered to families who have previously had a child with a metabolic disease or who are in a defined ethnic group. For example, testing for Tay-Sachs disease is relatively common in the Ashkenazi Jewish population. Countries that perform screening for metabolic diseases at birth typically test for up to 10 different conditions. Tandem mass-spectrometry is a new technology that allows for the detection of multiple abnormal metabolites almost simultaneously, making it possible to add approximately 30 disorders to the list of conditions for which newborns may be tested. If an infant is known to have a metabolic disorder soon after birth, appropriate therapy can be started early, which may result in a better prognosis. Some metabolic disorders respond very well if treatment is introduced at an early age. However, others have no effective therapy and cause severe problems, despite early diagnosis. In the future, gene therapy may prove successful in the treatment of some of these diseases.

Metabolic diseases are quite rare individually, but they are relatively common when considered as a group. Specific metabolic disorders have incidences ranging from approximately 1 in 500 (or even higher in isolated populations) to fewer than 1 in 1,000,000. As a group, it has been estimated that metabolic disorders affect approximately 1 in 1,000 individuals.

In 1908 British physician Sir Archibald Garrod postulated that four inherited conditions of lifelong duration—alkaptonuria, pentosuria, albinism, and cystinuria—were caused by defects in specific biochemical pathways due to the diminished activity or complete lack of a given enzyme. He called these disorders "inborn errors of metabolism." Although Garrod was incorrect in his categorization of cystinuria, his insights provided the field of biochemical genetics with a solid foundation, and the list of inherited inborn errors of metabolism has rapidly grown. This article is primarily concerned with these inherited metabolic diseases, although other disorders, including endocrine diseases (e.g., diabetes mellitus and hypothyroidism) and malnutrition (e.g., marasmus and kwashiorkor), also affect cellular metabolism. Food is broken down in a series of steps by cellular enzymes (proteins that catalyze the conversion of compounds called substrates) into products with a different biochemical structure. These products then become the substrate for the

next enzyme in a metabolic pathway. If an enzyme is missing or has diminished activity, the pathway becomes blocked, and the formation of the final product is deficient, resulting in disease. Low activity of an enzyme may result in the subsequent accumulation of the enzyme's substrate, which may be toxic at high levels. In addition, minor metabolic pathways that usually lie dormant may be activated when a substrate accumulates, possibly forming atypical, potentially toxic, products. Each cell in the body contains thousands of metabolic pathways, all of which are interlinked to some extent, so that a single blockage may affect numerous biochemical processes.

The consequences of metabolic imbalance may be severe; intellectual disability, seizures, decreased muscle tone, organ failure, blindness, and deafness may occur, depending on which enzyme is dysfunctional. In recent years, it has become apparent that even some conditions associated with multiple congenital anomalies (e.g., Smith-Lemli-Opitz syndrome) have an underlying metabolic cause.

The molecular blueprint for nearly all enzymes, structural proteins, cellular transport proteins, and other constituents that are responsible for carrying out the complex reactions involved in metabolism is stored as deoxyribonucleic acid (DNA) in the nucleus of the cell. A small amount of DNA of critical importance to metabolism also is contained in cellular organelles called mitochondria. DNA is organized into smaller units, termed genes, which direct the production of specific proteins or enzymes. In 1945 American geneticists George Beadle and Edward Tatum proposed a central tenet of molecular biology, the "one gene-one enzyme" principle, which states that a single gene directs the synthesis of a single enzyme. This principle has been refined to account for the fact that not all gene products are enzymes and that some enzymes are composed of multiple structural units encoded by different genes. Nevertheless, the one gene-one enzyme theory had immediate implications when applied to Garrod's initial theories regarding inborn errors of metabolism. Inherited metabolic diseases were postulated to occur when a gene is mutated in such a way as to produce a defective enzyme with diminished or absent function. In 1948 methemoglobinuria became the first human genetic disease to be identified as being caused by an enzyme defect. In 1949 American chemist Linus Pauling and colleagues demonstrated that a mutation causes a structural alteration in a protein; hemoglobin (the protein in red blood cells that carries oxygen to the tissues of the body) extracted from normal human red blood cells was shown to behave differently from hemoglobin taken from persons with the hereditary disease sickle-cell anemia. Thus, it was determined that mutant genes that direct the formation of abnormal proteins with altered function cause inborn errors of metabolism.

Inheritance

The inheritance of inborn errors of metabolism is most often autosomal recessive, meaning that two mutant genes are required to produce the signs and symptoms of disease. The parents of an affected child are most often asymptomatic carriers, because 50 percent of normal enzyme activity is adequate to maintain sufficient health. When two carriers of a deleterious trait produce offspring, however, there is a 25 percent chance of having an affected child, a 25 percent chance of having a child without the mutant allele, and a 50 percent chance of having a child who is also a carrier. In genetic terms, the carrier of an autosomal recessive condition has only one mutant gene (heterozygous), while an affected individual has two mutant genes (homozygous). All human beings have approximately six recessive mutant alleles in their genomes, but it is relatively rare for an individual to mate with someone who carries a mutation in the same gene. However, in cases of parental consanguinity, there is an increased risk of having a child with an autosomal recessive condition, because a common genetic background is shared.

Unlike autosomal recessive diseases, autosomal dominant diseases are expressed when only one mutant gene is present. These disorders show a strong family history, unless the condition arose from a new spontaneous mutation in an individual. A heterozygous individual has a 50 percent chance of passing the disorder to his offspring. Individuals with autosomal dominant disorders show a wide spectrum of disease severity, and carriers of a dominant trait may even appear asymptomatic.

Genetic material in the nucleus is found packed into DNA-protein complexes called chromosomes. Females have two X chromosomes, while males have an X and a Y chromosome. If a mutant gene is part of the X chromosome, the resulting disease is called X-linked. All male offspring who inherit an X-linked mutation are affected, because the Y chromosome of the XY pair does not have a compensating normal gene. Because the mutation is on the X chromosome and males transmit only the Y chromosome to their sons during fertilization, fathers do not transmit the disease to their sons. They can, however, transmit the carrier state (i.e., the mutant X chromosome) to their daughters. A heterozygous female carrier, meanwhile, has a 50 percent chance of producing a carrier daughter or affected son.

X-linked inheritance is complicated by the process of X chromosome inactivation (lyonization) in females. Although females carry two X chromosomes, early in embryonic development one of the X chromosomes is inactivated in each cell. The process of X chromosome inactivation is usually random, resulting in the formation of two cell lines in a given female who carries an X-linked disease mutation; one cell line has an inactivated normal X chromosome, and the other has an inactivated abnormal X chromosome. However, it is possible that a higher proportion of normal X chromosomes will be inactivated in a given individual, with the resultant appearance of symptoms of disease in various degrees. Such females are known as manifesting heterozygotes. Examples of X-linked disorders include ornithine transcarbamylase deficiency (an enzyme deficiency resulting in high blood levels of ammonia and impaired urea formation), X-linked adrenoleukodystrophy (a disorder that is characterized by progressive mental and physical deterioration and adrenal insufficiency), and Lesch-Nyhan syndrome (a disorder of purine metabolism that is characterized by the excretion of large amounts of uric acid in the urine, neurological disturbances, and self-mutilation).

The transmission of genes that are located in mitochondria (i.e., not contained in the nucleus of the cell) is termed maternal (mitochondrial) inheritance. Mitochondrial DNA (mtDNA), although much smaller than nuclear DNA, is critical in cellular metabolism. Most of the energy required by a cell to drive its metabolism is produced in mitochondria by proteins in a series of electron donor-acceptor reactions that make up the electron-transport, or respiratory, chain. Mitochondria are located in the cytoplasm of the ova and are inherited from the mother. Spermatozoa also have mitochondria, but these do not become incorporated into the developing embryo. When a cell divides, the mitochondria are randomly distributed to daughter cells. Each mitochondrion contains 2 to 10 copies of mtDNA, and each cell contains numerous mitochondria. In a given cell of a person with a mitochondrial disorder, the number of normal mitochondria may be greater than the number of abnormal mitochondria, and the cell may function well. On the other hand, if a cell contains a significant percentage of abnormal mitochondria, this cell and any tissue containing many such cells will exhibit impaired function. Affected children may demonstrate a spectrum of abnormalities, from appearing normal or mildly affected to being severely compromised, depending on the degree of mitochondrial dysfunction and the extent of tissue involvement.

Disorders of amino acid metabolism

Twenty amino acids, including nine that cannot be synthesized in humans and must be obtained through food, are involved in metabolism. Amino acids are the building blocks of proteins; some also function as or are synthesized into important molecules in the body such as neurotransmitters, hormones, pigments, and oxygen-carrying molecules. Each amino acid is further broken down into ammonia, carbon dioxide, and water. Disorders that affect the metabolism of amino acids include phenylketonuria, tyrosinemia, homocystinuria, non-ketotic hyperglycinemia, and maple syrup urine disease. These disorders are autosomal recessive, and all may be diagnosed by analyzing amino acid concentrations in body fluids. (Maple syrup urine disease also features the production of organic acids and is discussed in the section Organic acidemias.)

Phenylketonuria (PKU) is caused by decreased activity of phenylalanine hydroxylase (PAH), an enzyme that converts the amino acid phenylalanine to tyrosine, a precursor of several important hormones and skin, hair, and eye pigments. Decreased PAH activity results in accumulation of phenylalanine and a decreased amount of tyrosine and other metabolites. Persistent high levels of phenylalanine in the blood in turn result in progressive developmental delay, a small head circumference, behaviour disturbances, and seizures. Due to a decreased amount of the pigment melanin, persons with PKU tend to have lighter features, such as blond hair and blue eyes, than other family members who do not have the disease. Treatment with special formulas and with foods low in phenylalanine and protein can reduce phenylalanine levels to normal and maintain normal intelligence. However, rare cases of PKU that result from impaired metabolism of biopterin, an essential cofactor in the phenylalanine hydroxylase reaction, may not consistently respond to therapy.

Classic (hepatorenal or type I) tyrosinemia is caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme in tyrosine catabolism. Features of classic tyrosinemia include severe liver disease, unsatisfactory weight gain, peripheral nerve disease, and kidney defects. Approximately 40 percent of persons with the disorder develop liver cancer by the age of 5 if untreated. Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), a potent inhibitor of the tyrosine catabolic pathway, prevents the production of toxic metabolites. Although this leads to improvement of liver, kidney, and neurological symptoms, the occurrence of liver cancer may not be prevented. Liver transplantation may be required for severe liver disease or if cancer develops. A benign, transient neonatal form of tyrosinemia, responsive to protein restriction and vitamin C therapy, also exists.

Homocystinuria is caused by a defect in cystathionine beta-synthase (or β-synthase), an enzyme that participates in the metabolism of methionine, which leads to an accumulation of homocysteine. Symptoms include a pronounced flush of the cheeks, a tall, thin frame, lens dislocation, vascular disease, and thinning of the bones (osteoporosis). Intellectual disability and psychiatric disorders also may be present. Approximately 50 percent of persons with homocystinuria are responsive to treatment with vitamin B_6 (pyridoxine), and these individuals tend to have a better intellectual prognosis. Therapy with folic acid, betaine (a medication that removes extra homocysteine from the body), aspirin, and dietary restriction of protein and methionine also may be of benefit. Non-ketotic hyperglycinemia is characterized by seizures, low muscle tone, hiccups, breath holding, and severe developmental impairment. It is caused by elevated levels of the neurotransmitter glycine in the central nervous system, which in turn are

caused by a defect in the enzyme system responsible for cleaving the amino acid glycine. Drugs that block the action of glycine (e.g., dextromethorphan), a low-protein diet, and glycine-scavenging medications (e.g., sodium benzoate) may ease symptoms, but there is no cure for this severe condition. Liver cells play a critical role in disposing of nitrogenous waste by forming the compound urea (the primary solid component of urine) through the action of the urea cycle. When an amino acid is degraded, the ammonia nitrogen at one end of the molecule is split off, incorporated into urea, and excreted in the urine. A defect in any of the enzymes of the urea cycle leads to a toxic accumulation of ammonia in the blood. This, in turn, causes poor feeding, vomiting, lethargy, and possibly coma in the first two or three days of life (except in the case of arginase deficiency, which presents later in childhood).

Urea cycle defects are autosomal recessive, meaning they are passed on to offspring only when both parents carry the defect. One exception is ornithine transcarbamylase (OTC) deficiency, which is X-linked (and therefore causes severe disease in males who inherit the mutant X chromosome). However, OTC deficiency can also affect females who are “manifesting heterozygotes” (*see* the section Inheritance), presenting with severe disease during infancy or later in life during times of metabolic stress—for instance, during viral illness or childbirth. Emergency management of urea cycle disorders includes intravenous ammonia-scavenging medications and hemodialysis to decrease the blood ammonia level. Long-term therapy consists of a low-protein diet, the provision of nutrients deficient in these disorders, and phenylbutyrate or benzoate (medications that rid the body of excess ammonia). Persons with urea cycle disorders are at risk for recurrent crises with elevated ammonia levels, especially during times of infection; untreated or repeated episodes of high ammonia levels may cause intellectual disability and developmental impairment. Liver transplantation can cure some of these disorders. Amino acid transport disorders

Energy is required to move many amino acids from the intestinal tract into the blood or to reclaim them from the urine by special cells in the kidney. This transport of amino acids does not involve enzymes in metabolic pathways but rather transport proteins embedded in cellular or intracellular organelle membranes. Mutant proteins with decreased transport activities may prevent the absorption of dietary amino acids or cause their loss in the urine. For example, in cystinuria there is increased excretion of cystine, ornithine, arginine, and lysine in urine, which results in kidney stones. Cystinosis is characterized by the defective egress of cystine out of cellular organelles called lysosomes owing to a defect in the transporter cystinosin; persons with this disorder develop corneal deposits and kidney disease, and kidney transplantation may be necessary. Defective membrane transport of lysine, arginine, and ornithine in the intestines causes lysinuric protein intolerance (LPI), a disorder characterized by protein intolerance, diarrhea, unsatisfactory weight gain, osteoporosis, and rashes; late complications of LPI include kidney and lung disease. Hartnup disease is a disorder of amino acid transport in the intestines and kidneys; ataxia, a photosensitive rash, and mental abnormalities are the main symptoms.

Organic acidemias

Organic acids are carbon-based compounds that appear at abnormally elevated levels when metabolic pathways involving specific enzymes are blocked. Organic acidemias are conditions characterized by the accumulation of organic acids in body tissues and fluids, especially urine. The most common of these disorders are autosomal recessive conditions that involve the metabolism of the branched-chain amino acids leucine, isoleucine, and valine. Organic

acidemias share many features, including increased acid in the blood (acidemia), low blood sugar (hypoglycemia), low white blood cell count (neutropenia), poor growth, and varying degrees of mental impairment. These disorders may manifest in infancy or later in childhood.

Propionic acidemia is caused by a deficiency of the enzyme propionyl-CoA carboxylase, which results in an accumulation of propionic acid. Individuals with this disorder usually present with life-threatening illness early in infancy. Acidemia, dehydration, low white blood cell count, low muscle tone, and lethargy progressing to coma are typical features. The level of ammonia in the blood also may be high, because abnormal metabolites inhibit the urea cycle from functioning properly. The main therapies for propionic acidemia are dietary restriction of branched-chain amino acids, carnitine supplementation, and vigorous treatment of metabolic crises with intravenous fluids, glucose, and bicarbonate.

Persons with the classic form of methylmalonic acidemia (MMA), caused by a defect in the enzyme methylmalonyl-CoA mutase, have symptoms similar to individuals with propionic acidemia but may also develop the long-term complication of kidney failure. A combined liver-kidney transplant may be beneficial in some patients with severe kidney disease. One form of classic MMA responds to treatment with vitamin B_{12}. Rarer forms are caused by defects in the processing of vitamin B_{12} and often present later in childhood with progressive neurological impairment.

Maple syrup urine disease (MSUD) is a disorder of branched-chain amino acid metabolism that leads to the accumulation of leucine, isoleucine, valine and their corresponding oxoacids in body fluids—one result being a characteristic maple syrup smell to the urine of some patients. The disorder is common in the Mennonites of Pennsylvania. The classic form of MSUD presents in infancy with lethargy and progressive neurological deterioration characterized by seizures and coma. Unlike most organic acidemias, prominent acidemia is rare. Treatment involves restricting proteins and feeding with formulas deficient in the branched-chain amino acids. Persons with MSUD may have intellectual disability despite therapy, but early and careful treatment can result in normal intellectual development. Milder forms of MSUD may be treated with simple protein restriction or administration of thiamin (vitamin B_1).

Disorders of carbohydrate metabolism

The metabolism of the carbohydrates galactose, fructose, and glucose is intricately linked through interactions between different enzymatic pathways, and disorders that affect these pathways may have symptoms ranging from mild to severe or even life-threatening. Clinical features include various combinations of hypoglycemia (low blood sugar), liver enlargement, and muscle pain. Most of these disorders can be treated, or at least controlled, with specific dietary interventions.

Galactose and fructose disorders

Galactosemia usually is caused by a defective component of the second major step in the metabolism of the sugar galactose. When galactose is ingested, as in milk, galactose-1-phosphate accumulates. Therefore, the clinical manifestations of galactosemia begin when milk feeding is started. If the feeding is not stopped, infants with the disorder will develop lethargy, jaundice, progressive liver dysfunction, kidney disease, and weight loss. They are also susceptible to

severe bacterial infections, especially by *Escherichia coli*. Cataracts develop if the diet remains galactose-rich. Intellectual disability occurs in most infants with galactosemia if the disorder is left untreated or if treatment is delayed. Therapy is by exclusion of galactose from the diet and results in the reversal of most symptoms. Most children have normal intelligence, although they may have learning difficulties and a degree of intellectual disability despite early therapy.

Hereditary fructose intolerance (HFI) is caused by a deficiency of the liver enzyme fructose-1-phosphate aldolase. Symptoms of HFI appear after the ingestion of fructose and thus present later in life than do those of galactosemia. Fructose is present in fruits, table sugar (sucrose), and infant formulas containing sucrose. Symptoms may include failure to gain weight satisfactorily, vomiting, hypoglycemia, liver dysfunction, and kidney defects. Older children with HFI tend to avoid sweet foods and may have teeth notable for the absence of caries. Children with the disorder do very well if they avoid dietary fructose and sucrose.

Fructose 1,6-diphosphatase deficiency is associated with an impaired ability to form glucose from other substrates (a process called gluconeogenesis). Symptoms include severe hypoglycemia, intolerance to fasting, and enlargement of the liver. Rapid treatment of hypoglycemic episodes with intravenous fluids containing glucose and the avoidance of fasting are the mainstays of therapy. Some patients require continuous overnight drip feeds or a bedtime dose of cornstarch in order to control their tendency to develop hypoglycemia.

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