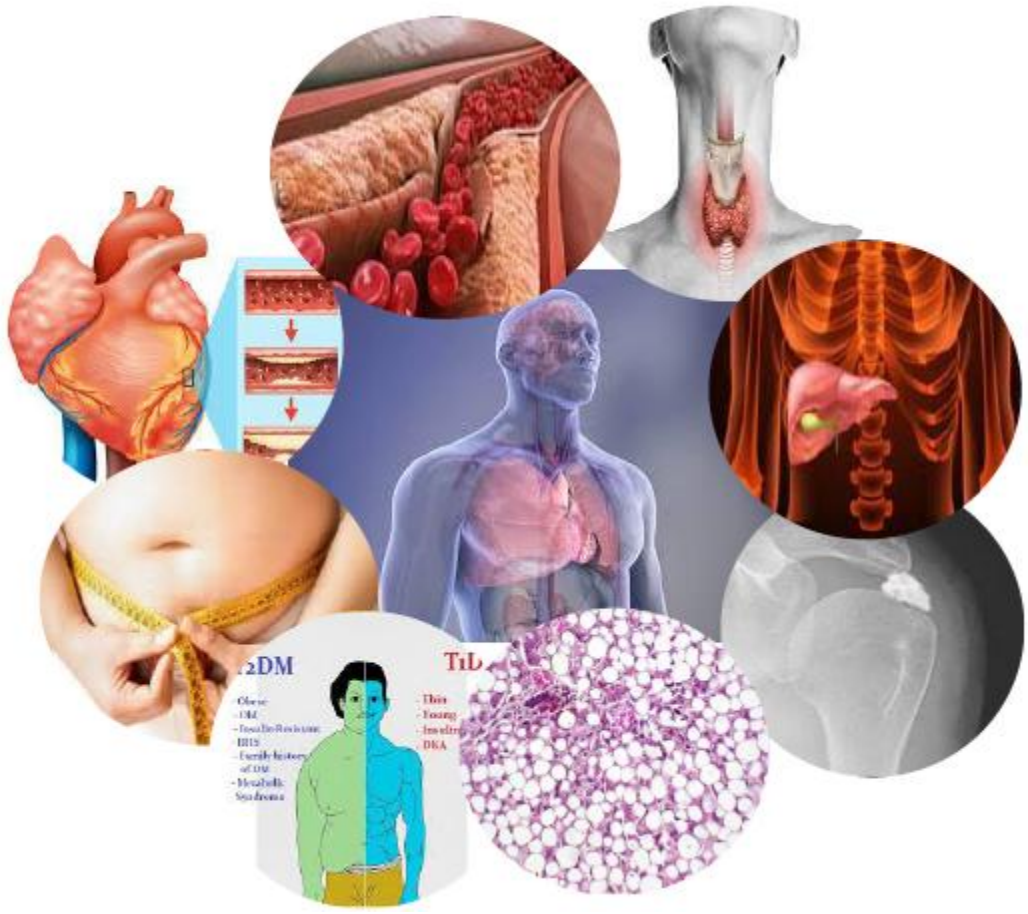
People's Democratic Republic of Algeria
Ministry of Higher Education and Research Scientist
Echahid Hamma Lakhdar El Oued University
Faculty of Natural and Life Sciences



COURS OF METABOLISM AND METABOLIC PATHOLOGIES

Dr TOUMI IKRAM

Summary

Introduction

Metabolism, the sum of the chemical reactions that take place within each cell of a living organism and that provide energy for vital processes and for synthesizing new organic material. The flux of nutrients along each metabolic pathway is governed chiefly by two factors: (1) the availability of substrates on which pacemaker, or key, enzymes of the pathway can act and (2) the intracellular levels of specific metabolites that affect the reaction rates of pacemaker enzymes. Key enzymes are usually complex proteins that, in addition to the site at which the catalytic process occurs (i.e., the active site), contain sites to which the regulatory metabolites bind. Interactions with the appropriate molecules at these regulatory sites cause changes in the shape of the enzyme molecule. Such changes may either facilitate or hinder the changes that occur at the active site. The rate of the enzymatic reaction is thus speeded up or slowed down by the presence of a regulatory metabolite.

Living organisms are unique in that they can extract energy from their environments and use it to carry out activities such as movement, growth and development, and reproduction. 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).

An abnormality in cell metabolism (or metabolic pathology) can result in abnormal accumulation (by deposition) in cells and / or in intercellular spaces of a substance. This substance can be endogenous or exogenous and is either normally present in small quantities (eg pigment) or absent in the normal state. In some cases the cell produces the substance, in other cases it accumulates the abnormal substance from elsewhere. There is therefore a break between intake and excretion, and / or synthesis and catabolism. This abnormal metabolism causes the substance to accumulate.

There is a wide variety of metabolic pathologies. Many metabolic disorders have little or no morphological translation (in the absence of complications) (not necessarily visible on imaging or on biopsies, for example). In most cases, the morphological manifestations are due to the accumulation of substances.

1. Metabolic syndrome

Metabolic syndrome means in its definition the presence of several associated metabolic abnormalities (abdominal obesity, hyper-triglyceridemia, low HDL-cholesterol, glucose intolerance or type 2 diabetes where it predisposes both to the onset of type 2 diabetes 2 and cardiovascular complications, hypertension) or even properly speaking it is not a disease. It is the combination of several physiological and metabolic disorders. It is relatively common with a prevalence which increases with the age of individuals. However, its prevention is based on early management of sedentary lifestyle and overweight.

It should be noted that the combination of components of the metabolic syndrome increased the cardiovascular risk regardless of the level of LDL-cholesterol.

Numerous biological abnormalities are associated with the metabolic syndrome such as an increase in the proteins of inflammation and in particular of the reactive C protein, pathological microalbuminuria, an increase in the plasminogen inhibitor (PAI-1) responsible for a reduction in fibrinolysis, hyperuricaemia.

Beyond hypertriglyceridemia and hypo-HDLemia which constitute defining criteria, other abnormalities in lipid metabolism are observed: increase in the plasma concentration of VLDL (very low density lipoprotein) and IDL (intermediatedensity lipoprotein)), presence of small and dense LDL. These abnormalities explain at least in part the increased cardiovascular risk associated with the metabolic syndrome. Small, dense LDL particles are more easily oxidized and are considered particularly atherogenic.

2. Origins of metabolic disease

2.1 Metabolic pathways

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.

2.2 Inheritance

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.

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.

3. 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.

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 B6

(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.

4. 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.

Deficiencies in the intestinal and/or renal transport of amino acids may be nonsymptomatic or cause symptoms because of deficient absorption of essential amino acids (e.g., tryptophan in Hartnup disease) or because of increased urinary concentration of unsoluble amino acids which causes nephrolithiasis (e.g., cysteine in cystinuria). These disorders are diagnosed by the quantitative analysis of amino acids in plasma and urine. Treatment depends on the clinical picture.

Deficiency of essential amino acids is treated by supplementation with large amounts of these compounds or, in the case of tryptophan deficiency, supply of the cofactor nicotinic acid that is normally synthesized from tryptophan. Renal calculi in cystinuria can be prevented by treatment with a chelating agent such as penicillamine, which forms mixed disulfi des with cysteine, and calculi once formed can be resorbed if they have not incorporated too much calcium.

5. Urea cycle defects

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 (figure 1).

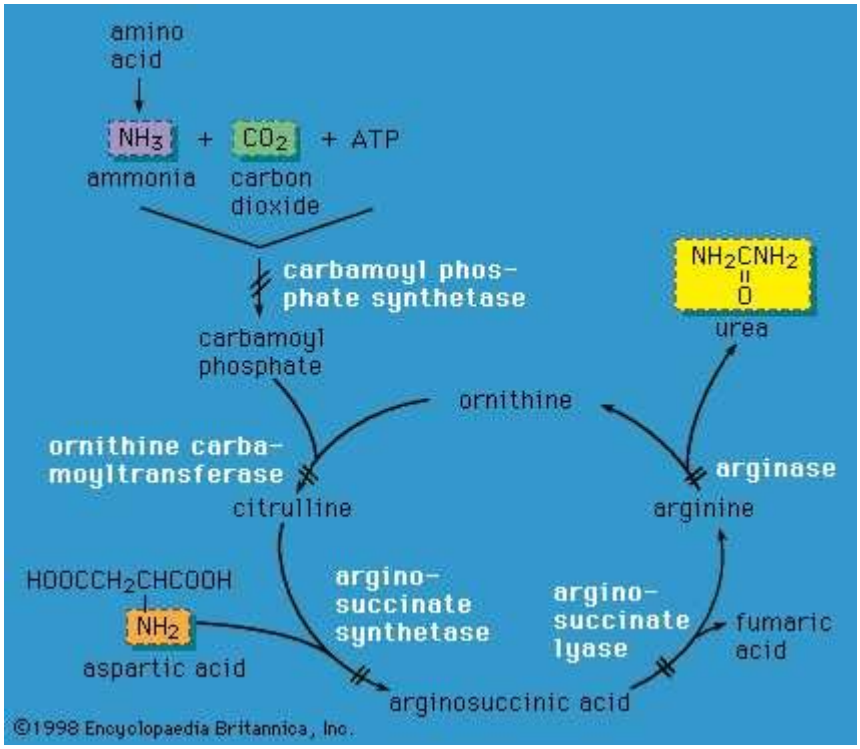


Figure 1: Urea cycle defects

6. Disorders of Ammonia (Detoxification)

The breakdown of protein produces large amounts of nitrogen in the form of ammonia that is highly neurotoxic but is normally converted to urea and excreted in the urine. Defects in enzymes of the urea cycle and other disorders of ammonia detoxification present clinically with encephalopathy and other symptoms of hyperammonemia.

Metabolic investigations should include analysis of the amino acids in plasma and urine as well as urinary orotic acid. Treatment requires the reduction of protein intake in conjunction with the supplementation of essential amino acids, the avoidance of catabolic states, and the administration of benzoate and/or phenylacetate/phenylbutyrate which remove nitrogen in the form of alternative conjugates of amino acids such as glycine and glutamine

7. Disorders of peptide metabolism

• The tripeptide glutathione and the gammaglutamyl cycle have multiple functions in cellular metabolism, ranging from amino acid transport across membranes to detoxifi cation of peroxides. Defi ciencies may cause neurological and hematological as well as metabolic problems. Investigations should include the determination of organic acids in the urine and

glutathione in various body fl uids. Treatment is largely symptomatic; certain drugs should be avoided.

•Defective breakdown of dipeptides of histidine such as homocarnosine or carnosine may be found in patients with intellectual disability although the causative relationship is uncertain. Ulcers of the skin, particularly of the legs, are seen in prolidase defi ciency. Investigations should include amino acid and peptide analysis of the urine.

8. 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 B12. Rarer forms are caused by defects in the processing of vitamin B12 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 B1).

9. 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.

9.1 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.

9.2 Glycogen storage disorders

The brain, red blood cells, and inner portion of the adrenal gland (adrenal medulla) depend on a constant supply of glucose for their metabolic functions. This supply begins in the small intestine, where transport proteins mediate the uptake of glucose into cells lining the gut. Glucose subsequently passes into the bloodstream and then the liver, where it is stored as glycogen. In times of starvation or fasting or when the body requires a sudden energy supply, glycogen is broken down into glucose, which is then released into the blood. Muscle tissue also has its own glycogen stores, which may be degraded during exercise. If enzymes responsible for glycogen degradation are blocked so that glycogen remains in the liver or muscle, a number of conditions known as glycogen storage disorders (GSD) can arise. Depending upon which enzyme is affected, these conditions may affect the liver, muscles, or both. In GSD type I (von Gierke disease), the last step in glucose release from the liver is defective, leading to hypoglycemia. Therapy consists of supplying continuous glucose to the digestive tract (e.g., by continuous drip feedings) during infancy and early childhood.

As the child grows, an improvement in symptoms tends to occur. Adequate glucose is supplied by frequent feedings of carbohydrates and slow-release glucose (uncooked cornstarch) before bedtime. Liver transplantation may also be curative, but this drastic measure is reserved for the small percentage of patients who do not respond to the usual treatment or who develop liver cancer. For the muscular forms of the disease, avoidance of strenuous exercise is the usual therapy. Defects in earlier steps in glycogen breakdown in the liver cause GSD types III, IV, VI, and IX, which usually lead to milder versions of type I

disease. Pompe disease (GSD type II) is discussed in the section Lysosomal storage disorders.

In addition to glycogen degradation, glucose may be manufactured from amino acids and pyruvate in the process of gluconeogenesis. Key enzymes in the gluconeogenic pathway include carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6-diphosphatase. Persons with defects in these enzymes develop conditions including fasting hypoglycemia, lactic acidemia, and liver enlargement. Thus, gluconeogenesis disorders may be difficult to distinguish from glycogen storage disorders at first presentation.

9.3 Congenital disorders of glycosylation

Congenital disorders of glycosylation (CDG; formerly known as carbohydrate-deficient glycoprotein syndrome) are recently described diseases that affect the brain and many other organs. The primary biochemical defects of CDG are in the N-glycosylation pathway that occurs in the cytoplasm and endoplasmic reticulum, cellular organelles involved in the synthesis of proteins and lipids. A defect in a mannose-processing enzyme, phosphomannomutase 2, causes the most common form of CDG (type I). Other enzymatic defects have been identified, but the biochemical bases of some CDG subtypes have not yet been determined. The classic form of CDG (type Ia) is characterized by low muscle tone in infancy, severe developmental delay, and brain abnormalities. Children with type Ia also have inverted nipples and an unusual distribution of fat, especially in the suprapubic region and buttocks. Other features include hypoglycemia, seizures, stroke-like episodes, retinal damage, impaired heart contractility, vomiting, liver disease, diarrhea, and a bleeding tendency. No effective therapy exists for CDG, except for the rare type Ib disease (phosphomannose isomerase deficiency), in which oral administration of mannose may reverse symptoms in some cases.

10. Disorders of lipid metabolism

Lipids are large, water-insoluble molecules that have a variety of biological functions, including storing energy and serving as components of cellular membranes and lipoproteins. Cells that line the small intestine absorb dietary lipids and process them into lipoprotein particles that enter the circulation via the lymphatic system for eventual uptake by the liver. Triglycerides, cholesterol, and fat-soluble vitamins are transported through the blood by these lipoprotein particles (figure 2).

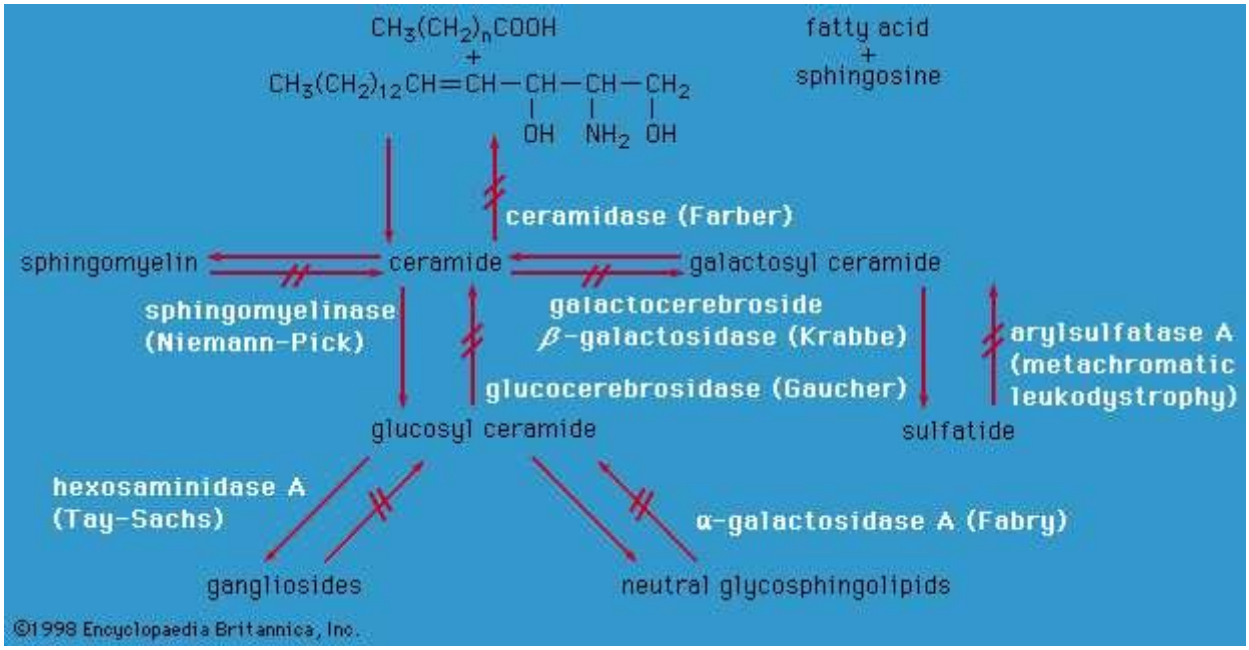


Figure 2: lipid metabolism disorders

10.1.Lipoprotein disorders

The major classes of lipoproteins are chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Disorders that affect lipid metabolism may be caused by defects in the structural proteins of lipoprotein particles, in the cell receptors that recognize the various types of lipoproteins, or in the enzymes that break down fats. As a result of such defects, lipids may become deposited in the walls of blood vessels, which can lead to atherosclerosis (a disease characterized by abnormal thickening and hardening of the walls of the arteries).

Familial hypercholesterolemia is an autosomal dominant disease that is caused by the deficiency of the LDL receptor on the surface of cells in the liver and other organs. As a result, cholesterol is not moved into the cells. Under normal conditions, when enough cholesterol is present in the cell, feedback mechanisms signal enzymes to cease cholesterol synthesis. In familial hypercholesterolemia, these enzymes are relieved of feedback inhibition, thus inducing the production of still more cholesterol. The disease is characterized by early coronary vascular disease, strokes, and fatty deposits on the tendons. Blood cholesterol levels are very high from birth, and LDL cholesterol is also elevated. Treatment is by a low-cholesterol diet and drugs that inhibit cholesterol synthesis or increase its excretion in the gastrointestinal tract.

If a person with familial hypercholesterolemia is homozygous for the condition, severe vascular disease starts in early childhood, and heart attacks are usual by the age of 20. Similar symptoms are present in familial dysbetalipoproteinemia (hyperlipoproteinemia type III), which may be inherited as an autosomal recessive or autosomal dominant condition (that is, if the trait has been inherited from both parents). In this disorder, which manifests in adulthood, increased blood cholesterol and triglycerides are present due to an abnormality of a constituent of lipoproteins called apoprotein E. Treatment is similar to that required for familial hypercholesterolemia.

A deficiency of microsomal transfer protein causes abetalipoproteinemia, an autosomal recessive condition characterized by the virtual absence of VLDL and LDL. Triglycerides accumulate in the gastrointestinal tract and liver, and there are low blood levels of cholesterol, HDL cholesterol, and triglycerides. Persons with abetalipoproteinemia have severe fat malabsorption and develop neurological symptoms including unsteady gait, retinal defects, and nerve damage due to the deficiency of vitamin E.

10.2.Disorders of Fatty Acid

Oxidation and Ketogenesis Mitochondrial fatty acid oxidation is required for the provision of energy during fasting, either through complete oxidation or through production of ketones in the liver that then serve as an alternative energy source for the brain. Disorders in this pathway typically present as hypoketotic hypoglycemia precipitated by fasting, leading to coma or epileptic seizures. In addition, some disorders cause severe liver disease and/or cardiomyopathy probably as a result of the accumulation of toxic metabolites. The diagnosis is best reached in the acute situation through the analysis of free fatty acids and the ketone bodies

3-hydroxybutyrate and acetoacetate, as well as the acylcarnitine profi le and urinary organic acids. The diagnosis may be missed if samples are obtained in the normal interval between episodes or after the patient has been treated with intravenous glucose. Treatment consists of avoidance of fasting. Carnitine supplementation is mostly unnecessary and must be carefully balanced in some defects, particularly those that cause cardiomyopathy or hepatopathy.

10.3.Fatty acid oxidation defects

During prolonged starvation, the metabolism of fats stored in adipose tissue is needed for energy production. After the glycogen stores have been depleted, both gluconeogenesis and the production of ketone bodies by liver fatty acid beta-oxidation (or β-oxidation) are essential for providing energy for the brain. The oxidation of fatty acids for energy occurs in the mitochondria of liver cells and requires a carrier molecule, carnitine, which is synthesized in the body and is also obtained from the dietary intake of animal products such as meat, milk, and eggs. Some fatty acid oxidation disorders arise through dysfunction of carnitine transport enzymes, although most of these conditions are caused by fat-degrading enzymes directly involved in the beta-oxidation cycle itself. In individuals with inherited disorders of carnitine transport, a deficiency of carnitine may cause severe brain, liver, and heart damage. Treatment with carnitine is partially effective. Fatty acid oxidation disorders are relatively common and as a group may account for approximately 5 to 10 percent of cases of sudden infant death syndrome (SIDS). The disorders commonly manifest with hypoglycemia, liver disease, decreased muscle tone, and heart failure (cardiomyopathy).

Children with medium-chain acyl-CoA dehydrogenase deficiency (MCAD) appear completely normal, unless they fast for a prolonged period or are faced by other metabolically stressful conditions, such as a severe viral illness. During periods of metabolic stress, affected individuals may develop hypoglycemia, lethargy, vomiting, seizures, and liver dysfunction. Intravenous hydration and glucose must be given in a timely fashion, otherwise the disease can be fatal. However, if hydration and nutrition are monitored closely, children with MCAD lead a relatively normal life. Therapy consists of carnitine administration and avoidance of excessive fat intake. Other fatty acid oxidation disorders may respond to similar therapy, but in general, their prognosis is not as good.

Long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency may present with heart failure, hypoglycemia, multi-organ system failure, and retinal pigmentary changes. A fetus with LCHAD deficiency can induce liver disease during pregnancy in a mother who is a heterozygous carrier for the condition. This appears to be due to a combination of the metabolic demands of pregnancy, the lack of enzyme activity in the fetus, and the reduced activity of the enzyme in the mother, causing enough of an imbalance in the usual energy pathways to result in the storage of fat in the maternal liver.

11. Mitochondrial disorders

The mitochondrial respiratory chain consists of five multi-subunit protein complexes that produce the majority of energy driving cellular reactions. Dysfunction of the respiratory chain leads to decreased energy production and to an increase in the production of toxic reactive oxygen species. In addition, damaged mitochondria release apoptotic factors, which act as signals to induce cell death. Respiratory chain proteins are formed by the concerted action of both nuclear and mitochondrial genes. Therefore, mitochondrial disorders may be inherited in either a Mendelian (autosomal recessive, autosomal dominant, or X-linked) or maternal (mitochondrial) fashion, because mutations may occur in either the nuclear or mitochondrial genome.

Disorders of energy metabolism (usually summarized as mitochondrial disorders although enzymes deficient in organic acidurias or fatty acid oxidation disorders are also located in the mitochondrion) comprise a rapidly increasing number of molecularly defined diseases that cause primary or secondary impairment of the production of adenosine triphosphate (ATP).

Affected proteins include subunits of the respiratory chain complexes; components of the final pathways of substrate breakdown such as the pyruvate dehydrogenase complex and the Krebs cycle; at least 24 chaperones for the production of respiratory chain complexes; components of mitochondrial deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis; numerous proteins involved in cofactor biosynthesis; as well as various other components of mitochondrial homeostasis. Mitochondrial disorders typically manifest with symptoms and signs of an energy defi ciency and a highly variable pattern of organ dysfunctions. In many cases, there are lactic acidemias and progressive neurodegenerative disease.

Periods of metabolic stress such as intercurrent infections may trigger a deterioration of the patient’s condition. The diagnostic work-up may be diffi cult and should include frequent measurements of blood lactate levels, cerebrospinal fl uid (CSF) lactate, plasma amino acids and alanine, and often a search for mutations in mitochondrial DNA. Repeated, careful examinations of organ functions as well as imaging are essential. Recently, exome sequencing has emerged as the primary diagnostic approach in many patients. Treatment options are limited but usually include various vitamins and cofactors such as ribofl avin,

coenzyme Q, or thiamine. Heterozygous mutations in the genes of some Krebs cycle enzymes (e.g., fumarase) cause inherited cancer predisposition syndrome.

The signs and symptoms of mitochondrial disorders are dependent on the severity of the mutation, the percentage of dysfunctional mitochondria, and the energy requirements of the affected tissues. Patients with mitochondrial disorders may present with a bewildering array of symptoms, because any tissue in the body may be affected at any point in an individual's lifetime. However, prominent involvement of the nervous and muscular systems is common because these tissues are highly dependent on mitochondrial metabolism. Patients often have biochemical markers of underlying disease (for example, an elevated blood lactate level or unusual organic acids in the urine), but some patients have completely normal metabolic screens. Often the diagnosis of mitochondrial disorders requires demonstration of respiratory chain dysfunction by the measurement of complex activities in muscle tissue obtained from a biopsy. So-called muscle ragged red fibres may be seen on microscopic examination and are suggestive of mitochondrial disease, but often are not present and may be seen in other muscle disorders. Sometimes a diagnosis can be made by identifying an mtDNA mutation through molecular diagnostic techniques. However, not all mutations are known, and it is impractical to perform a complete analysis of an individual's mtDNA. Furthermore, because some mitochondrial disorders may be caused by mutations present in the nuclear DNA, screening of nuclear genes that code for mitochondrial respiratory gene subunits ultimately may be necessary to pinpoint the underlying cause of a patient's symptoms; however, such an exhaustive search is not practical.

Defective mitochondrial membrane ion transporters, transmembrane carrier proteins, and intramitochondrial metal homeostasis may also cause mitochondrial disorders. Neurodegenerative disorders including Friedreich ataxia and Wilson disease have been associated with aberrant mitochondrial metal metabolism; impaired iron homeostasis is present in Friedreich ataxia, while copper metabolism is abnormal in Wilson disease. The respiratory chain is affected secondarily in these conditions. Mitochondrial respiratory chain dysfunction also has been theorized to play a role in more common neurodegenerative diseases such as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig disease), as well as in normal aging. However, evidence of the role of mitochondrial dysfunction in these conditions and in normal aging is inconclusive. There is no proven therapy for patients with respiratory chain disorders, though

various dietary supplements and cofactors have been tried, and experiments have begun in the area of gene therapy.

12. Lysosomal Storage Disorders

Lysosomes are cytoplasmic organelles in which a variety of macromolecules are degraded by different acid hydrolase enzymes. Lysosomal enzymes are coded for by nuclear DNA and are targeted to lysosomes by specific recognition markers. If a lysosomal enzyme is absent or has reduced activity or if enzymes are not correctly targeted to lysosomes, the macromolecules normally degraded by lysosomes will accumulate, causing abnormal storage of various complex compounds including glycolipids, glycosaminoglycans, oligosaccharides, and glycoproteins. Lysosomal storage disorders are autosomal recessive, except for Fabry disease and Hunter syndrome, which are X-linked. Abnormal macromolecule storage leads to a variety of signs and symptoms, depending on where the storage occurs. Some diseases (e.g., Gaucher disease type I) usually affect only peripheral tissues such as the liver, spleen, or bone, others affect only the central nervous system (e.g., Tay-Sachs disease), while yet others affect both brain and systemic organs (e.g., Niemann-Pick disease).

Characteristics of many lysosomal storage disorders include coarsening of facial features, eye abnormalities, enlarged liver and spleen, and bone disease. As a group, these conditions cause severe neurological impairment, often starting in infancy. However, each disease often has a spectrum of severity depending on the degree of enzymatic compromise. For example, although Tay-Sachs disease is often fatal in early. childhood, some forms do not present until adulthood. Most lysosomal storage disorders have no therapy, except for supportive care. The difficulty with most therapies is that they do not enter the brain, because of the presence of the so-called blood-brain barrier. Bone marrow transplantation has been attempted in individuals with lysosomal storage disorders, but overall results have been disappointing. Successful therapy for disorders without central nervous system involvement has been accomplished; Gaucher disease type I, for example, is responsive to enzyme replacement therapy, that is, frequent intravenous infusions of the specific enzyme that is missing in the disorder, and encouraging results have been reported in Fabry disease and Pompe disease (GSD type II).

13. Peroxisomal disorders

Peroxisomes are cytoplasmic organelles that play a central role in the catabolism of very-long-chain fatty acids and other compounds through the process of beta-oxidation. They also are critical in the biosynthesis of important cellular membrane constituents (plasmalogens), cholesterol, and bile acids. Unlike mitochondria, peroxisomes do not contain DNA, therefore all of the components of their enzyme systems and membrane proteins are coded for by the nucleus. Most peroxisomal disorders exhibit autosomal recessive inheritance, with the exception of the X-linked form of adrenoleukodystrophy. They usually present with severe neurological compromise, but other organ systems—for example, bone and kidneys—may also be affected. No specific treatment exists for these disorders, and nearly all are lethal early in their course.

Some disorders feature a reduced number or complete absence of peroxisomes, which results in severely depressed activity of peroxisomal functions, affecting the functions of numerous enzymes. Such disorders include Zellweger (cerebrohepatorenal) syndrome, neonatal adrenoleukodystrophy, hyperpipecolic acidemia, and infantile Refsum disease. Patients may have severely decreased muscle tone (hypotonia), cerebral malformations, seizures, and an enlarged liver in infancy. Many develop eye abnormalities, in particular a defect in retinal pigment. Patients with Zellweger syndrome also may have small kidney cysts and cranial abnormalities.

In other disorders peroxisomes appear normal, with decreased activity of only a single enzyme. One example is X-linked adrenoleukodystrophy (X-ALD), an insidious disorder in which affected individuals show normal early development. Between the ages of 4 and 8, behaviour problems including hyperactivity, aggressiveness, or poor school performance appear in affected boys. Children often lose speech, memory skills, and the ability to walk, and seizures occur late in the course of the disease. The skin may have a brownish hue due to adrenal insufficiency. Other forms of X-ALD may not include neurological disease, or neurological complications may be mild (adrenomyeloneuropathy). Classic severe X-ALD and adrenomyeloneuropathy may coexist in the same family. Lorenzo's oil (named after the patient who inspired its development), a mixture of trioleate and trierucate oils, improves or completely corrects the elevation of very-long-chain fatty acids in blood, but it does not have an effect on the neurological progression of the disease because it does not cross the blood-

brain barrier. Some success has been reported in patients treated by bone marrow transplantation early in the course of disease.

14. Purine and pyrimidine disorders

Purines and pyrimidines are essential building blocks of DNA, RNA, and compounds involved in cellular energy transfer and biosynthetic reactions (e.g., adenosine triphosphate, ATP). Purine and pyrimidine disorders have a wide spectrum of signs and symptoms, including autism, kidney stones, susceptibility to infections, and severe intellectual disability. Symptoms may present from infancy to old age. Most metabolic screening tests do not detect disorders of purine or pyrimidine metabolism; hence, they must be specifically sought out by having specialized analyses performed.

Adenosine deaminase (ADA) deficiency results in the accumulation of 2′-deoxyadenosine in the circulating white blood cells (lymphocytes). This, in turn, causes a decreased number of lymphocytes and a drastically increased susceptibility to infection (severe combined immunodeficiency, SCID). Bone marrow transplantation may be curative, and gene therapy has shown promise, but enzyme replacement therapy is the standard treatment. Lesch-Nyhan syndrome is an X-linked condition caused by a deficiency in the enzyme hypoxanthine-guanine phosphoribosyltransferase. The nervous system is affected, resulting in writhing movements in the first year of life, after a period of normal development. A particularly troublesome feature is the occurrence of self-mutilation. Intellectual disability is also common. Most individuals with Lesch-Nyhan syndrome excrete a large amount of uric acid in their urine, leading to gout, kidney stones, and possible kidney failure. A high fluid intake and the drug allopurinol are helpful in treating the joint and kidney problems, but have no effect on the severe intellectual disability. Physical restraint and extraction of the teeth are the only successful therapies for the self-injurious behaviour.

15. Porphyrias

Porphyrins are intermediate molecules in the biosynthetic pathway of heme, a complex molecule that carries oxygen in red blood cells (as part of hemoglobin) and takes part in liver detoxification reactions. Porphyrins display fluorescence when exposed to ultraviolet light. Disorders of heme biosynthesis, the porphyrias, present with neurological symptoms, intermittent abdominal pain, nausea, and vomiting. They are distinguished by a dark or red appearance of the urine. Porphyrias that primarily affect red blood cells tend to cause photosensitivity and blistering skin rashes, while those that affect the liver are more

commonly associated with gastrointestinal symptoms. Unlike most metabolic diseases, many of the porphyrias are autosomal dominant conditions. Many patients with enzyme defects in the heme biosynthetic pathway remain asymptomatic, which is unusual for inborn errors of metabolism.

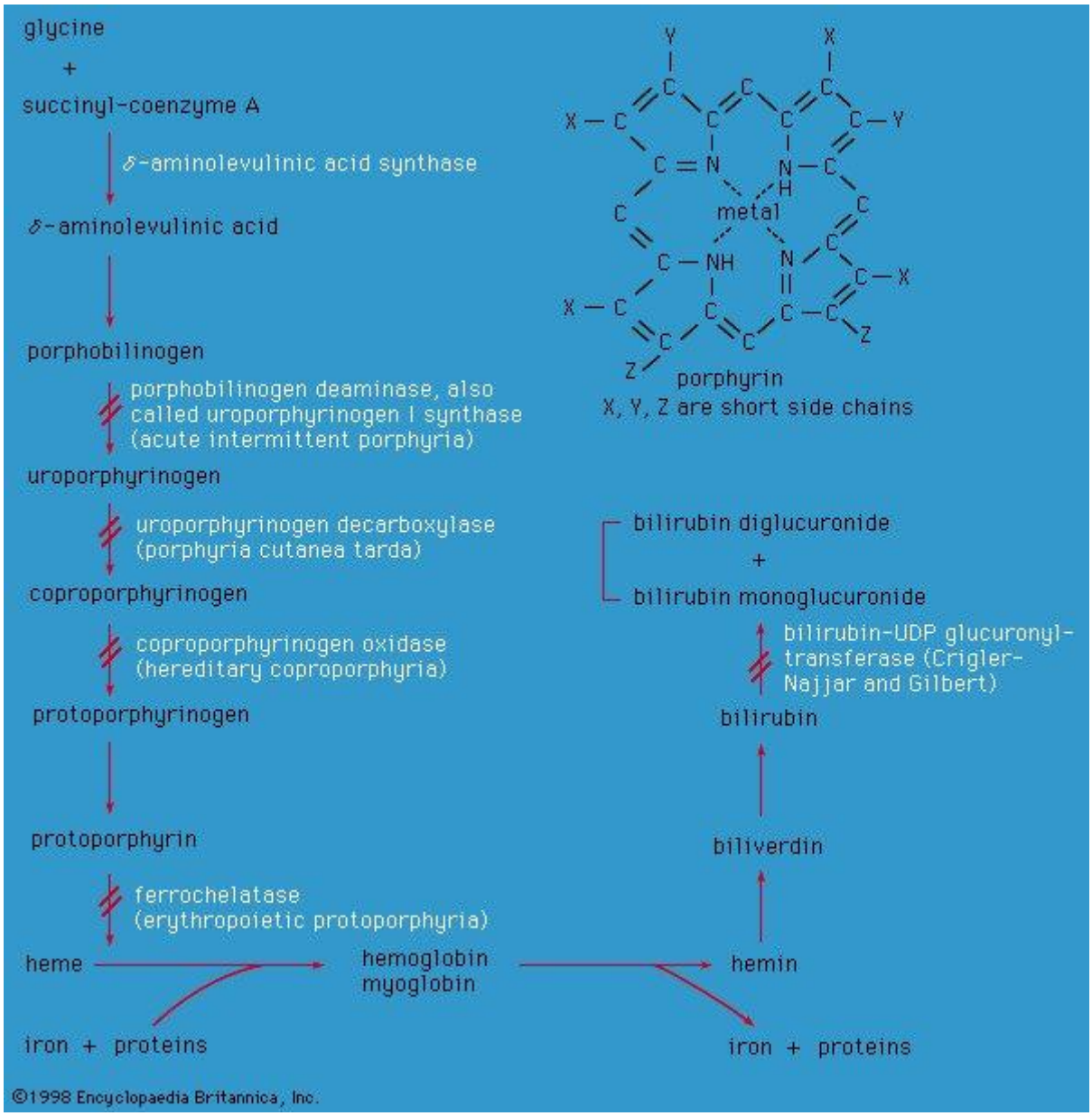


Figure 3: Disorders of heme biosynthesis

Eight different porphyrias have been identified. One common form is acute intermittent porphyria, which is caused by a deficiency of the enzyme porphobilinogen deaminase. Symptoms usually arise during adolescence, and hormonal changes (e.g., menstruation), alcohol ingestion, certain foods, and some drugs may exacerbate the condition (figure 3).

Diagnosis is made by detecting porphyrins in the urine. Treatment is by administration of heme during acute attacks. A high-carbohydrate diet may also be of benefit.

16. Disorders of cobalamin and folate metabolism

Genetically determined or nutritional deficiencies of vitamin cofactors may affect various metabolic pathways and cause a wide range of clinical symptoms. They can frequently be satisfactorily treated by supplementation of the deficient substance. Of particular importance in intermediary metabolism are cobalamin (vitamin B 12) and folate which are essential for cytosolic methyl group transfer. The cellular methylation reactions require methyl group transfer from serine to S adenosylmethionine involving the folate cycle, the cobalamin (vitamin B 12), and the methionine–homocysteine cycle. A disturbance in this pathway may be caused by methylcobalamin deficiency, a disturbance of the folate cycle, or by deficient remethylation of homocysteine to methionine. Most disorders of cobalamin metabolism as well as nutritional deficiency of vitamin B 12 cause methylmalonic aciduria. Clinically, disorders of cytosolic methyl group transfer cause an encephaloneuropathy, often with additional hematological problems such as megaloblastic anemia and thromboembolic complications of hyperhomocysteinemia. The diagnosis involves the analysis of urinary organic acids, plasma amino acids (homocysteine), and levels of folate and cobalamin. Treatment includes supplementation of cobalamin and folate, in some situations with addition of betaine and methionine.

17. Disorders of the transport or utilization of copper metabolism

Wilson disease causes a chronic hepatopathy and symptoms of central nervous dysfunction, while patients with Menkes disease suffer from neurological problems in conjunction with abnormalities of the hair, connective tissue, and bones. Diagnosis involves the analysis of copper and coeruloplasmin in serum, urine, and liver tissue. Treatment in Wilson disease is aimed at reducing copper load, while copper should be parenterally substituted in Menkes disease. A well-characterized variant of Menkes disease that is associated with milder mutations in the ATP7A gene is the occipital horn syndrome, also known as X-linked cutis laxa. Another gene required for normal copper homeostasis has recently been identified based on the presence of abnormalities of copper metabolism found in an autosomal recessive disorder called MEDNIK (mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma) syndrome (OMIM: 609313). The phenotype combines clinical features of both Wilson and Menkes diseases.

18. Disorders of the transport or utilization manganese

Patients have been reported with typical features of Wilson disease, including a liver dysfunction and a movement disorder that result from mutations in a manganese transporter and consequently hypermanganesemia.

19. Disorders of the transport or utilization of iron

Patients affected with such disorders may present with iron deficient anemia, e.g., due to insufficient intestinal absorption of iron, or with iron overload and liver dysfunction as in hemochromatosis. Secondary iron overload may be observed in some hemolytic anemias. Treatment is directed at substitution or removal of iron.

20. Disorders of the transport or utilization of zinc

Acrodermatitis enteropathica is characterized by chronic skin problems, alopecia, and central nervous symptoms. It is diagnosed through reduced levels of zinc and alkaline phosphatase and is treated with supplementation of zinc.