Metabolic Diseases of the Nervous System

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I. Glucose Transporter Type 1 Deficiency
II. Menkes Disease
III. Segawa Disease (Dopa-Responsive Dystonia)
IV. Disorders of Pyruvate Metabolism
V. Glycosylation Disorders
VI. Organic Acidurias
VII. Urea Cycle Disorders
VIII. Galactosemia
IX. Phenylketonuria
X. Lesch-Nyhan Disease
XI. Pantothenate Kinase Deficiency
XII. Smith-Lemli-Opitz Syndrome

Metabolic disorders constitute an expanding group of flux diseases that includes heterogeneous conditions (see Table 10.1). Thus, a unifying definition becomes necessary. Strictly speaking, neurometabolic diseases arise from genetic deficiency of intermediary metabolism enzymes, in contrast with mutations in genes encoding cytostructural proteins or proteins involved in cell division, immunity, excitability, cell-to-cell communication, secretion or movement, which are not counted among them. Nevertheless, intermediary metabolism abnormalities can be found in virtually all these conditions, allowing for the consideration of at least some when discussing the neurometabolic diseases.

Whether involving carbohydrate, lipid, or protein metabolism, the manifestations of neurometabolic diseases are pleomorphic and can present at any time during the entire lifespan. Regardless of their age of onset and mode of presentation, the practical approach to the patient afflicted by a neurometabolic disease includes a customized but systematic series of evaluations, as well as an assessment of the ancestry and family structure aimed at identifying a possible pattern of inheritance and detecting all relatives at-risk for a potentially heritable trait. It is often possible to establish the pattern of inheritance of a familial disease on clinical grounds alone. In the case of a potentially heritable trait, apparently unaffected relatives can be found to manifest subtle abnormalities indicative of an incompletely penetrant trait. A series of analytical investigations are performed to confirm the diagnosis according to the patient’s clinical syndrome. The biochemical analysis of patient tissues, such as biopsied muscle, and of cellular elements, such as cultured fibroblasts, is often necessary to confirm a specific enzyme deficiency and is followed, when available, by genotyping. In some cases, genetic test batteries or panels are available to screen genes associated with diseases that share a similar phenotype. Genotyping allows for genetic counseling, for the screening of relatives at risk and, in an increasing number of instances, for prenatal diagnosis via amniocentesis.
Disorders of cell membranes impact cell communication and the exchange of substances with the environment by disrupting membrane proteins or the small molecules that serve as ligands. Transport disorders, caused by primary deficiency of proteins responsible for selective permeability, cause particularly widespread cellular abnormalities that derive from secondary intracellular substrate or cofactor deficiency. Disorders that cause abnormal neurotransmission include, apart from membrane receptor diseases, neurotransmitter synthesis and recycling deficiencies that render cell membranes unexcitable or abnormally modulated. Disorders of transporters include abnormalities in transporter production or movement, or in membrane function or composition, leading to their accumulation or malformation and to the buildup of nonmetabolized compounds, or, in the special case of mitochondrial diseases, to deficient energy production. Enzymatic disorders are due to mutation of soluble enzymes or to cofactor deficiencies caused by inadequate absorption, processing, or binding, resulting in abnormal catalysis.

The cellular abnormalities brought about by soluble enzyme deficiencies tend to be morphologically modest but functionally widespread, reflecting cellular substrate diffusion, and associate with the release (or deprivation) of circulating plasmatic compounds, a feature used in the diagnosis of these diseases. A further category includes disorders of nuclear metabolism (DNA and RNA synthesis and processing, DNA methylation and repair) and of protein synthesis that are associated with broad cellular abnormalities owing to the central mission that the nucleus and the ribosome carry out in the cell. Some of these disorders are covered in other sections of this work.

In general, membrane disorders tend to be associated with milder disease phenotypes, organelle disorders with slowly accumulating abnormalities, enzyme disorders with marked
biochemical abnormalities detectable in tissues and fluids, and nuclear disorders with a vast array of cellular alterations and phenotypes.

Metabolic diseases follow any imaginable temporal course even in the absence of environmental or nutritional precipitating factors, with some conditions manifesting only periodically and others exhibiting a static or apparently immutable course, in contrast with the common notion of metabolic diseases as unrelenting, continuously symptomatic processes. The basis for the apparently paradoxical static and episodic manifestations of neurometabolic diseases is provided by the compartmentalization of metabolism. Because all cellular functions are spatially limited and regulated by membranes, net catalysis occurs at rates governed not only by enzyme kinetics, but also (and often mainly) by substrate availability and product abundance. The former process, dependent on enzyme structure, is dictated by the gene; the latter, by the ability of cells and organelles to distribute and clear substrates and products, a process that is inherently dependent on membrane function (Hubert et al., 2005).

Multiple cellular compartments situated in various cell types participate in a typical metabolic pathway (Hofmeyr & Cornish-Bowden, 1991). Thus, for example, an enzymatic deficiency affecting a reaction that is constantly active may be associated with the accumulation of a substrate that interferes with other reactions, causing inhibition and resulting abnormal cell function. Such a substrate may be eliminated from the cell after it reaches a certain threshold level at a rate that is dependent on its concentration. Once the substrate first accumulates, production and elimination proceed indefinitely, maintaining a constant (elevated) concentration in the cell. Such may constitute the basis for the permanent, immutable clinical manifestations that are sometimes associated with a static metabolic abnormality. Episodic diseases can also be understood within the same mechanistic framework: a compound may accumulate silently until a threshold concentration is reached or until another slowly fluctuating cellular process renders the cell susceptible, such that additional reactions are triggered, causing a decompensation later followed by the restoration of the original (unstable) equilibrium.

Prenatal molecular diagnosis accomplished via sampling of fetal tissue obtained by chorionic biopsy is available for numerous metabolic diseases. Biochemical or molecular genetic assays of amniocytes are available for an increasing number of conditions. Yet, the most effective mode of detection is by voluntary screening of populations at risk. Several reproductive and therapeutic options are available when a pathogenic mutation is detected, including testing of an early embryo after in vitro fertilization before implantation, in vitro fertilization by a healthy donor, nuclear transfer or early initiation of therapy of an affected newborn. Newborn screening using tandem mass spectrometry applied to dried blood can detect many—if not most—metabolic disorders, including specific disorders of amino acid, organic acid, and fatty acid metabolism (Chance & Kalas, 2005). Conditions universally screened for include phenylketonuria and congenital hypothyroidism, being possible to avoid their vast impact on the developing nervous system (Therrell et al., 1992). Neurometabolic diseases can also be diagnosed postmortem using dry blood cards and skin punch biopsies from which live fibroblast cultures can be established for use in biochemical and genetic assays (Christodoulou & Wilcken, 2004).

The principles of molecular therapy are based on the use of alternative enzyme pathways, the facilitation of enzyme function by cofactor administration, enzyme replacement, and genomic modulation. Gene replacement therapy remains an elusive ideal as difficulties related to targeting, maintenance, and expression of the corrected gene construct have not been solved. Diets that diminish the utilization of a deficient metabolic pathway can be administered enterally or infused parenterally. Diets containing low protein, low carbohydrate or high glucose sometimes with extra fat supplementation meeting minimum calorific and protein and essential amino acid requirements are available for specific diseases. Cofactors and vitamins are administered at high doses when a vitamin-responsive disorder is suspected. Parenteral enzyme infusions are used with some success in lysosomal storage diseases such as Fabry disease, Gaucher disease, mucopolysaccharidosis type I, and Pompe disease (Brady & Schiffmann, 2004). Bone marrow transplantation corrects the enzymatic deficiencies of cells of hematopoietic origin in some mucopolysaccharidoses and, in some cases, the enzyme activity can be partially restored in the brain. Early transplantation may prevent progression of neurological disease but its long-term benefits are obscured by residual problems such as progression of skeletal and joint disability. Hepatic and liver–kidney transplantation have been considered in a variety of disorders with mixed overall success. Pharmacological stimulation of residual alleles or unrelated genes using histone deacetylation inhibitors, and loosening of translational fidelity by aminoglycoside antibiotic derivatives, applied to mutations that result in the generation of premature DNA termination codons.

The following sections are devoted to select neurometabolic diseases that exemplify diverse modes of transmission, mechanism, and clinical features.

I. Glucose Transporter Type 1 Deficiency

Mutations in the SLC2A1 gene, which codes for Glut1, the facilitative carrier responsible for the transport of glucose through the blood brain barrier and through astrocyte membranes, cause Glut1 deficiency syndrome. In its typical form, manifestations include infantile epilepsy, spasticity and ataxia (De Vivo et al., 1991). The disease, an example
of a haploinsufficient state, can be inherited as an autosomal dominant trait from oligosymptomatic adults, who may experience only infrequent seizures or mild neuropsychological disturbances. Glut1 deficiency can lead to particularly severe neurological disability when SLC2A1 mutations (located in chromosome 1) compound in both alleles, a rare occurrence. Newly recognized phenotypes such as isolated ataxia or dystonia, both partially responsive to carbohydrate load or to a ketogenic diet, have received increased attention, as the full phenotypic spectrum of the disease continues to be expanded (Wang et al., 2005). The hallmark feature and main diagnostic parameter associated with the disease is hypoglychorrhachia: a diminished CSF glucose concentration, usually below 40 mg/dl or 2.2 mM. Supportive evidence of Glut1 deficiency is provided by a characteristic cerebral PET pattern, revealing a globally diminished uptake of fluoro-deoxyglucose with marked thalamocortical depression and relative accentuation of basal ganglia tracer uptake (see Figure 10.1 and Pascual et al., 2002). The disease may be confirmed by assaying glucose uptake in patient erythrocytes, which are rich in Glut1, followed by sequence analysis of SLC2A1. The Glut1 transporter is a member of the Multiple Facilitator Superfamily (MFS), a large class of carriers that mediate the ATP hydrolysis-independent flow of diverse substrates driven by concentration gradients alone.

Three MFS members (a lactose permease, a glycerol phosphate transporter and an oxalate transporter) have been crystallized and their structures solved (Abramson et al., 2004). All three share a unique structural plan that includes 12 membrane spanning helical domains arranged in two globular, pseudosymmetrical six-helix domains. Some of the membrane helices are long and tilted and oriented such that the transporters appear to contain large water-filled extracellular and intracellular vestibules and interact directly with substrate only through a few residues contributed by the central portion of the inner core helices. The helices are thought to remain stable in place by flanking charges located at membrane boundaries. Numerous mutations have been identified and some mutational hotspots have been discovered in Glut1 deficiency patients. In particular, charged residues at helical boundaries are frequently mutated, leading to misfolding of the transporter or to the production of a carrier protein.

![Figure 10.1](image_url)

**Figure 10.1** Cerebral glucose uptake in Glut1 deficiency. Left side panels A–C: Axial, parasagittal, and coronal PET images of a normal 20-year-old male. Physiological distribution of the radiotracer is appreciable. D–F: Analogous images in Glut1 deficiency in a patient 1.6 years old. G–I: Similar images from a 31-year-old patient. Right side panels represent the glycosylated transporter inserted in the plasma membrane of the subjects presented in the left side, colored in red and labeled according to the presence of a mutation in the transporter. Wild type: no mutation; del969c, c971t: deletion of cytosine at nucleotide 969 resulting in a premature stop codon at 971; R126C arginine 126 to cysteine substitution.

*Source:* Juan M. Pascual, original illustration.
incapable of undergoing normal conformational changes. More severe (homozygous) loss of Glut1 function is incompatible with embryonic survival in mice and, probably, in men. Embryonic stem cells and zebrafish neural structures devoid of Glut1 manifest increased apoptosis (Heilig et al., 2003, Jensen et al., 2006).

The treatment of Glut1 deficiency may include dietary supplementation with carbohydrate-rich compounds to increase the glucose concentration gradient across the blood brain barrier, where the residual (normal) transporters arising from the normal allele function below maximum velocity, lipoic acid, thought to enhance the expression of Glut1, or the administration of a ketogenic diet to provide alternative energetic substrates, as the brain can readily import and consume circulating ketone bodies. The ketogenic diet controls seizures, and it can be administered early in infancy, well before the cerebral metabolic rate for glucose reaches its maximum and the brain relies on glucose metabolism. Nevertheless, it appears that some of the neurological abnormalities set in very early in infancy and that, despite the responsiveness of epilepsy to the ketogenic diet, significant cognitive and motor disability persists as invariant features of the disease.

II. Menkes Disease

Mutation of the copper ATPase transporter ATP7A (see Figure 10.2), located in the trans-Golgi network and encoded by the X chromosome, causes the progressive copper deficiency disorder Menkes disease (Menkes et al., 1962). Also known as kinky hair disease, Menkes disease is associated with impaired copper flux, in contrast with Wilson’s disease, which is characterized by copper excess in tissues such as brain and liver. ATP7A is ubiquitous and regulates the absorption of copper in the gastrointestinal tract (Menkes et al., 1999). Neonates affected by Menkes disease manifest seizures, hypothermia, and feeding difficulties. The infants are pale and display a characteristic kinky hair. ATP7A allows cellular copper to cross intracellular membranes and is translocated from the trans-Golgi network to the plasma membrane in the presence of extracellular copper.

Certain Menkes disease mutations specifically inhibit the copper-induced trafficking of otherwise normal functional copper transporters, a process that normally involves the formation of a phosphorylated transporter. This phosphorylated state is generated during the catalytic cycle of the pump and is recognized specifically for translocation, thus specifying

**Figure 10.2** Hypothetical structure of ATP7A based on hydropathy analysis. The protein includes eight membrane spanning domains and long cytoplasmic loops. Conserved residues are represented by circles.  
*From:* Schaefer & Gitlin (1999).  
*Figure Path:* http://ajpgi.physiology.org/cgi/content/full/276/2/G311.
the cellular location of the transporter. In the brain, neuronal glutamate receptor (NMDA type) activation results in trafficking of ATP7A to neuronal processes independently of intracellular copper concentration. This process is particularly important in hippocampal neurons, where a NMDA receptor-dependent, releasable pool of copper modulates neuronal activation. Copper chelation exacerbates NMDA-mediated excitotoxic cell death in hippocampal neurons, whereas the presence of copper is protective as it results in reduced cytoplasmic calcium levels after NMDA receptor activation. This phenomenon is dependent upon nitric oxide production by these neurons (Schlief et al., 2006).

In other tissues (including the brain), the fundamental abnormality is the maldistribution of copper, which is unavailable as a cofactor of several enzymes that include mitochondrial cytochrome c oxidase, lysyl oxidase, superoxide dismutase, dopamine beta-hydroxylase, and tyrosinase. Thus, the main features of the disease include mitochondrial respiratory chain dysfunction (complex IV deficiency), deficiency of collagen cross-links resulting in hair (pili torti and trichorrhexis nodosa) and vascular abnormalities (elongated cerebral vessels prone to rupture and hemorrhage), neuronal degeneration (markedly affecting Purkinje cells), and deficient melanin production. In patients, serum copper concentration is low and the ratio of urinary homovanillic acid/vanillylmandelic acid is elevated, constituting important diagnostic assays (Matsuo et al., 2005). A variety of minimally symptomatic phenotypes, including isolated ataxia or mental retardation, have been recognized. Intramuscular or subcutaneous administration of chelated copper-histidine affords protection against intellectual deterioration but is less effective in preventing other somatic complications (Christodoulou et al., 1998).

III. Segawa Disease (Dopa-Responsive Dystonia)

The neurotransmitter disorders represent an expanding group of signaling neurometabolic diseases. Several disturbances of monoamine and gamma-aminobutyric acid (GABA) metabolism presenting in infancy and childhood have been recognized and disorders involving additional neurotransmitters will probably be identified. Among the monoamine disorders, Segawa disease, aromatic L-amino acid decarboxylase deficiency, and tyrosine hydroxylase deficiency cause characteristic encephalopathies. Among the GABA disorders, pyridoxine-dependent seizures due to antiquitin gene mutations, GABA transaminase deficiency, and succinic semialdehyde dehydrogenase deficiency have been recognized (Hyland, 2003). Autosomal dominant mutations of the guanosine triphosphate cyclohydrolase I (GCH1) gene, located in chromosome 14, cause the treatable dystonic syndrome known as Segawa disease (Segawa et al., 2003).

The fundamental biochemical abnormality is a decrease of tetrahydrobiopterin (BH4) associated with reduced tyrosine hydroxylase activity, leading to deficient dopaminergic transmission and extrapyramidal dysfunction. A decrease in the tyrosine hydroxylase content and activity in the ventral striatum accompanies a decrease in dopamine release that results in hypoactive D1 receptors (see Figure 10.3).

Some GCH1 mutations decrease TH activity by deleterious, dominant negative interactions between the mutated subunit and the residual normal TH from the other allele (Ichinose et al., 1999). Normally, tyrosine hydroxylase-dependent synaptic activity fluctuates throughout the day and decreases after the third decade of life: this probably accounts for the marked diurnal progression of symptoms and for the clinical stabilization observed after the fourth decade. Initial symptoms are often gait difficulties due to involuntary foot equinovarus posturing. Postural dystonia and tremor and a small stature dominate the clinical symptomatology and can be prevented by administration of levodopa. Marked intrafamilial symptom severity variability exits and nondystonic family members may suffer from major depressive disorder or obsessive–compulsive disorder responsive to enhancers of serotonergic neurotransmission and to levodopa administration. Sleep disorders, including difficulty falling asleep, excessive sleepiness, and frequent disturbing nightmares, are also features of this patient population (Van Hove et al., 2006).

Autosomal recessive Segawa syndrome is due to mutations in the tyrosine hydroxylase gene and causes early-onset parkinsonism responsive to levodopa, a more severe phenotype. Measurement of both total biopterin (most of which exists as BH4) and neopterin (the byproduct of the GTPCH1 reaction) in cerebrospinal fluid reveals that both compounds are decreased, a useful diagnostic indicator of GCH1 deficiency. Decreased activity of GCH1 in stimulated mononuclear blood cells and fibroblasts further supports the diagnosis. An oral phenylalanine load can reveal a subclinical defect in phenylalanine metabolism due to liver BH4 deficiency in patients with Segawa disease.

IV. Disorders of Pyruvate Metabolism

Defects in the pyruvate dehydrogenase (PDH) complex are an important cause of lactic acidosis. PDH is a large mitochondrial matrix enzyme complex that catalyzes the oxidative decarboxylation of pyruvate to form acetyl-CoA, nicotinamide adenine dinucleotide (NADH), and CO₂. Symptoms vary considerably in patients with PDH complex deficiencies, and almost equal numbers of affected males and females have been identified, despite the location of the PDH E1 alpha subunit gene (PDHA1) in the X chromosome, owing to selective female X-inactivation. Thus, the mechanisms for the clinical variation observed in E1 alpha
deficiency patients and its resemblance to a recessive disease are mutation severity in males and the pattern of X-inactivation in females.

Several dozen PDHA1 mutations have been identified (Lissens et al., 2000). Patients harboring mutations in the E1 beta subunit, the E2 dihydrolipoyl transacetylase segment of the complex, the E3-binding protein, the lipoamide-containing protein X, and the PDH phosphatase have been reported (Maj et al., 2005). Neurodevelopmental abnormalities, microcephaly, epilepsy, and agenesis of the corpus callosum are characteristic features of E1 alpha deficiency (Nissenkorn et al., 2001). Infants may exhibit facial features of fetal alcoholic syndrome and older children can present with acute intermittent weakness and areflexia or with alternating hemiplegia. Episodic dystonia with hypotonia and ataxia and lesion of the globus pallidus can be caused by E2 deficiency. Diagnosis of these disorders requires measurements of lactate and pyruvate in plasma and cerebrospinal fluid, analysis of amino acids in plasma and organic acids in urine, as well neuroradiologic investigations, including magnetic resonance spectroscopy to detect lactate. Enzymatic analysis of fibroblast PDH activity can be performed and

Figure 10.3  Pathophysiology of Segawa disease. Affected neural structures are enclosed in thick lines. Solid lines represent disease-involved pathways; thick lines indicate activation and thin lines inhibition. Closed triangles indicate inhibitory influences and open triangles excitation. Shades structures and events are believed to be key for pathogenesis. TH, tyrosine hydroxylase; D1, D2 and D4, dopamine receptors subtypes; BH4, tetrahydrobiopterin; SNC, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; LGP, lateral globus pallidus; MGP, medial globus pallidus; STN, subthalamic nucleus; VL thalamus, nucleus ventralis lateralis thalamus; SC, superior colliculus; PPN, pedunculopontine nucleus.


Figure Path: http://www.sciencedirect.com/science?_ob=MiamiCaptionURL&_method=retrieve&uId=B6T50-4153152-C&_image=fig5&_ba=5&_coverDate=09%2F30%2F2000&_aiId=464057051&_doc=1&_fmt=full&_orig=search&_cdi=4988&_qd=1&view=c&_acct=C000002018&_version=1&_urlVersion=0&_userid=18704&md5=ebabdc817a05a06e6d5107333fa321.
molecular diagnosis is available. A ketogenic diet is recommended together with thiamine supplementation, which may provoke a substantial response (Duran & Wadman, 1985).

Pyruvate carboxylase deficiency is an autosomal recessive disease due to mutation of the PC gene, located in chromosome 11. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate in the presence of abundant acetyl-CoA, replenishing Krebs cycle intermediates in the mitochondrial matrix. The enzyme is a tetramer bound to biotin. PC is involved in gluconeogenesis, lipogenesis, and neurotransmitter synthesis. PC deficiency can present with three degrees of phenotypic severity: an infantile form (A) with infantile moderate lactic acidosis, mental and motor deficiencies, hypotonia, pyramidal tract dysfunction, ataxia, and seizures leading to death in infancy. Episodes of vomiting, acidosis, and tachypnea can be triggered by metabolic imbalance or infection (Robinson et al., 1996). A severe neonatal form (B), manifests with severe lactic acidosis, hypoglycemia, hepatomegaly, depressed consciousness, and severely abnormal development. Abnormal limb and ocular movements are common findings. Brain MRI reveals cystic periventricular leukomalacia. Hyperammonemia and depletion of intracellular aspartate and oxaloacetate are profound. Early death is common. A rare benign form (C) causes episodic acidosis and moderate mental impairment compatible with survival and near normal neurological performance. A variety of mutations have been identified, with mosaicism probably accounting for the less severe phenotypes. Enzymatic analysis of fibroblast PC activity can be performed, but molecular diagnosis can be complicated by mosaicism. Dietary modification with triheptanoin (a triglyceride) supplementation has been attempted as a means to increase acetyl-CoA and anaplerotic propionyl-CoA (Mochel et al., 2005). Liver transplantation has also been performed, with reversal of ketoacidosis and amelioration of lactic academia (Nyhan et al., 2002).

V. Glycosylation Disorders

Glycosylation produces different glycans (or glycoconjugates) that modify the structure and function of cellular proteins and lipids. Protein glycosylation leads to the formation of N-glycans, O-glycans, and glycosaminoglycans. N-glycans are linked to asparagine residues of proteins that are part of a specific recognition motif. The degradation of proteins and glycans involves endocytosis and trafficking to lysosomes. Defects in these catabolic steps include glycosidase deficiencies that cause storage diseases like Gaucher, Niemann-Pick type C, Sandhoff, and Tay-Sachs diseases. Congenital disorders of glycosylation (CDG) are a group of autosomal recessive diseases defined by abnormal glycosylation of N-linked oligosaccharides (Freeze & Aebi, 2005). Over a dozen genes coding for enzymes involved in the N-linked oligosaccharide synthetic pathway have been found to harbor mutations, causing a variety of disease manifestations.

In some cases, the phenotypes are incompletely known, as only a small number of patients have been studied. In addition, novel enzyme deficiencies are periodically reported. Thus, genotype:phenotype correlations are preliminary. CDG-Ia, the most common type of CDG, is due to phosphomannomutase 2 deficiency leading to insufficient synthesis of the glycosylation precursor dolichol-oligosaccharide. Salient manifestations include inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia. The clinical course has been divided into an infantile multisystem stage in which all somatic organs can be affected, a late infantile and childhood ataxia-with-mental retardation stage, during which neuropathy, retinitis pigmentosa, and stroke-like episodes can manifest, and an adult stable disability stage. CDG-Ib is caused by mannose phosphate isomerase deficiency. Salient features include cyclic vomiting, hyperglycemia, hepatic fibrosis, and protein-losing enteropathy, occasionally associated with coagulation disturbances without neurologic involvement. CDG-Ic is due to deficiency of man(9)GlcNAc(2)-PP-dolichyl-alpha-1,3-glucosyltransferase and is associated with hypotonia, intellectual deficits, ataxia, strabismus, and epilepsy. The diagnosis of all types of CDG can be reached analyzing serum transferrin glycoforms by isoelectric focusing to estimate the number of sialylated N-linked oligosaccharide residues associated to the protein (Jaeken & Carchon, 2004). In select cases, molecular genetic analysis is feasible, including prenatal diagnosis. CDG-Ib is the only treatable type of CDG: mannose supplementation normalizes hypoproteinemia and coagulation defects and reverses both protein-losing enteropathy and hypoglycemia.

VI. Organic Acidurias

The organic acidemias (or organic acidurias) are disorders characterized by the urinary excretion of nonamino organic acids, which result from the abnormal amino acid catabolism of branched chain amino acids or lysine. These disorders include, but are not limited to, maple syrup urine disease (MSUD), propionic acidemia, methylmalonic acidemia, isovaleric acidemia, 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, ketothiolase deficiency, glutaric aciduria type I, and succinyl semialdehyde dehydrogenase deficiency, among other less well-understood types (Ogier de Baunly & Saudubray, 2002). Specific enzymatic defects are responsible for each disorder, but several acidurias are caused by more than one enzyme deficiency. They are all inherited in an autosomal recessive fashion. The most severe and common presentation is a toxic neonatal encephalopathy. Newborns manifest vomiting, poor feeding, and progressive
neurologic symptoms such as seizures, abnormal tone, and progressively depressed consciousness leading to coma. Cerebral edema, leukoencephalopathy, perisylvian (opercular) hypotrophy, or basal ganglia necrosis are features frequently detectable in neuroimaging studies. Unrecognized children and adolescents can exhibit episodic ataxia, intellectual deficits, Reye syndrome, or psychiatric disturbances. Laboratory abnormalities include acidosis, ketosis, hyperammonemia, abnormal serum hepatic enzyme levels, hypoglycemia, and neutropenia. Secondary carnitine deficiency due to excessive excretion of acylcarnitine conjugates is common. The diagnosis is made by urine organic acid analysis, a technique that is particularly sensitive when it is performed during clinical decompensation, as the pattern of urinary excretion may be normal during symptom-free intervening periods. Analysis of plasma amino acids may also help to distinguish among specific disorders and direct enzyme activity measurements in lymphocytes or fibroblasts confirm the diagnosis. DNA sequence analysis is available for the most common disorders. Prenatal diagnosis relies on the analysis of amniotic fluid metabolites and it is simplified by DNA analysis in the context of a family in which a child has been previously diagnosed. Treatment relies on the replacement of enzyme substrates and precursors while meeting essential amino acid and caloric needs. Several special infant formulas are commercially available. Thiamine is used to treat thiamine-responsive MSUD and hydroxocobalamin to treat methylmalonic acidemia. Carnitine supplementation is used to correct secondary deficiency. In disorders of propionic acid metabolism, the peridiotic administration of antibiotics can reduce the production of propionate by intestinal flora (de Baulny et al., 2005). Hepatic or combined liver–renal transplantation has been attempted with moderate success in some of these disorders.

VII. Urea Cycle Disorders

The urea cycle disorders result from defects in the metabolism of nitrogen, which is predominantly produced during the breakdown of proteins and other nitrogen-containing molecules and transferred through ammonia into urea. The urea cycle is the only source of endogenous arginine and it is the main clearance mechanism for this waste nitrogen. Hyperammonemia is the defining feature of these disorders, that include deficiencies in the urea cycle enzymes carbamyl phosphate synthase I, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase and arginase, and in the cofactor producer N-acetyl glutamate synthetase (Leonard and Morris, 2002). With the exception of X-linked ornithine transcarboxylase deficiency, urea cycle disorders are inherited in an autosomal recessive fashion. These disorders manifest in the neonatal period with cerebral edema, lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, abnormal tone, respiratory alkalosis, and coma.

In milder (or partial) urea cycle defects, ammonia accumulation may be triggered by illness, protein load, fasting, valproate administration, or by other decompensations at any later age, resulting in mild elevations of plasma ammonia accompanying cyclical vomiting, lethargy, sleep disturbances, delusions, hallucinations, and psychosis. Slowly progressive spastic paraparesis and growth retardation can be manifestations of arginase deficiency. A subset of carrier females manifest ornithine transcarboxylase deficiency owing to skewed X-inactivation, a state that may also lead to hyperammonemic crises during pregnancy or in the postpartum. In a variety of urea cycle defects, the rates of total urea synthesis and the urea cycle-specific nitrogen flux (measured by mass spectrometry using 15N amide-labeled glutamine, which preferentially donates labeled nitrogen via carbamyl phosphate synthesis) correlate with phenotypic severity and predict carrier status in asymptomatic individuals (see Figure 10.4).

A specific pattern of plasma amino acid abnormalities allows a specific diagnosis. For example, glutamine, alanine, and asparagine are commonly elevated, whereas arginine may be reduced in all urea cycle disorders except in arginase deficiency, in which it is markedly elevated. Plasmatic citrulline and urinary orotic acid excretion also assist in dissecting the affected enzymatic pathway. Enzyme activity assays, usually performed in liver tissue, are reserved for confirmatory diagnosis, and DNA sequencing analysis is available for most of these disorders (Steiner & Cederbaum, 2001). The treatment during a crisis involves dialysis or other forms of plasma filtration aimed at reducing plasma ammonia concentration. Intravenous administration of arginine chloride and of the nitrogen scavengers sodium phenylacetate and sodium benzoate diminishes the accumulation of ammonia. Long-term administration of oral sodium phenylbutyrate and arginine increase the excretion of nitrogen by providing an alternative pathway (Batshaw et al., 2001). Nevertheless, dietary protein restriction constitutes the mainstay of maintenance therapy.

VIII. Galactosemia

The conversion of beta-D-galactose to glucose 1-phosphate is accomplished by the action of four enzymes that collectively constitute the Leloir pathway. In the first step of the pathway, beta-D-galactose is epimerized to alpha-D-galactose by galactose mutarotase. The second step involves the phosphorylation of alpha-D-galactose by galactokinase to yield galactose 1-phosphate. In the fourth step, UDP-galactose is converted to UDP-glucose by UDP-galactose 4-epimerase. Classic (type I) galactosemia is caused by deficiency of the third step enzyme galactose-phosphate
uridylyltransferase (GALT), which catalyzes the production of glucose-1-phosphate and uridyldiphosphate (UDP)-galactose from galactose-1-phosphate and UDP-glucose (Leslie, 2003). Mutations in the genes encoding for galactokinase or epimerase can give rise to forms of galactosemia. Classic galactosemia can be inherited in an autosomal recessive fashion and is always attributable to mutations in the GALT gene in chromosome 9 (Tyfield et al., 1999). Within days of starting to feed milk or lactose-containing formulas, affected infants experience feeding difficulties, hypoglycemia, hepatic dysfunction, bleeding diathesis, jaundice and hyperammonemia. When untreated, sepsis and death may occur. Those infants who survive but continue to ingest galactose develop intellectual deficits, cortical and cerebellar tract signs. Despite early initiation of dietary therapy, the long-term outcome can include cataracts, poor growth, language dysfunction, extrapyramidal signs and ataxia, and ovarian failure.

The diagnosis is established by measuring erythrocyte GALT activity and by isoelectric focusing of the enzyme. All newborn screening programs typically include galactosemia and thus, the disease should be readily identified before becoming symptomatic. Biochemical and molecular genetic testing are widely used for heterozygote detection and prenatal diagnosis. Assay of erythrocyte galactose-1-phosphate concentration, measurement of urinary galactitol and estimation of total body oxidative flux of $^{13}$C-galactose to $^{13}$CO$_2$ are utilized to quantify residual enzyme function and to monitor the response to dietary adjustments over time. The mainstay of therapy is lactose restriction, which rapidly reverses liver disease in newborns. Upon diagnosis, infants are immediately offered a lactose-free, soy-based formula that contains sucrose, fructose, and other non-galactose complex carbohydrates.

**IX. Phenylketonuria**

Classic phenylketonuria (PKU) is caused by near-complete deficiency of phenylalanine hydroxylase activity leading to hyperphenylalaninemia. The phenylalanine hydroxylase gene, PAH, is located in chromosome 12 and mutations in PAH are inherited in an autosomal recessive fashion. Over 250 missense mutations have been identified in the three domains (catalytic, regulatory, and tetramerization) of PAH (see Figure 10.5). PAH is assembled as a tetramer and as a dimer that coexist in interchangeable equilibrium. Each subunit contains an iron atom at the catalytic site. PKU mutations alter residues located at several enzyme regions: the active site, structural residues, residues involving inter-domain interactions in a monomer, residues that interact with the N-terminal autoregulatory sequence that extends over the active site in the catalytic domain, and residues at the dimer or tetramer interface regions of the structure.

PKU was the first metabolic cause of mental retardation to be identified and is routinely screened for in all newborns. It is also an example of a disorder fully treatable by dietary restriction. A small proportion of infants with hyperphenylalaninemia display impaired synthesis or recycling of tetrahydrobiopterin (BH4) in the presence of a normal PAH gene, a condition that is independently treatable (Blau & Erlandsen, 2004). Classical untreated PKU leads to microcephaly, epilepsy, and severe intellectual and behavioral...
X. Lesch-Nyhan Disease

Among the inherited disorders of purine and pyrimidine metabolism, Lesch-Nyhan disease, caused by hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is the most common. The enzyme, encoded by the HPRT1 gene in the X chromosome, catalyzes the conversion of hypoxanthine to inosinic acid (IMP) and of guanine to guanylic acid (GMP) in the presence of phosphoribosylpyrophosphate, recycling purines derived from DNA and RNA (Nyhan, 1997). HPRT1 mutations diminish enzyme function or abundance and lead to uric acid overproduction. In addition to suffering from hyperuricemia, hyperuricuria and renal stones, male patients manifest abnormal neurological development during infancy. Hypotonia and failure to accomplish early motor milestones such as sitting, crawling, or walking can be prominent features.

Later in childhood, other symptoms emerge, including abnormal involuntary movements such as dystonia, choreoathetosis, opisthotonus, and ballismus. Pyramidal tract dysfunction includes spasticity, hyperreflexia, and Babinski signs. Profound intellectual deficits and self-injurious behavior can be prominent as are other motor compulsions. Females are carriers of HPRT1 mutations and can manifest increased uric acid excretion. They may show symptoms of the disease when nonrandom X-chromosome inactivation or skewed inactivation of the normal HPRT1 allele occur (Jinnah et al., 2000). A urinary urate-to-creatinine ratio above 2 is characteristic of the disease, as is an excessive urinary excretion of urate.
Defective HPRT enzyme activity can be measured in blood cells, fibroblasts, or lymphoblasts. DNA sequencing detects mutations in virtually all cases. Treatment aims to restrain uric acid overproduction with allopurinol, which inhibits the conversion of hypoxanthine and xanthine to uric acid mediated by xanthine oxidase. Bone marrow transplantation seems to be of only limited value both in correcting hyperuricemia and improving neurobehavioral symptoms (Deliliers & Annaloro, 2005).

XI. Pantothenate Kinase Deficiency

Also known as pantothenate kinase-associated neurodegeneration (PKAN) and formerly called Hallervorden-Spatz disease, pantothenate kinase deficiency causes neuronal degeneration associated with cerebral iron accumulation. This disorder is caused by the absence of pantothenate kinase 2, which is encoded by the PANK2 gene located in chromosome 20, and participates in coenzyme A biosynthesis, catalyzing the phosphorylation of pantothenate (vitamin B5), N-pantothenoyl-cysteine, and pantotheine (Hayflick, 2003). Accumulation of N-pantothenoyl-cysteine and pantotheine may induce cell toxicity directly or via free radical damage by chelating iron. Deficient pantothenate kinase 2 may also be predicted to result in coenzyme A depletion and defective membrane biosynthesis in vulnerable cells such as rod photoreceptors (Johnson et al., 2004). Accumulation of iron is specific to the globus pallidus and substantia nigra. Axonal spheroids, thought to represent swollen axons secondary to defective axonal transport, appear in the pallidionigral system, in the subthalamic nucleus, and in peripheral nerves. Patients first manifest in early childhood with dystonia that interferes with ambulation, associated with dysarthria, rigidity, pigmented retinopathy, and pyramidal tract dysfunction with spasticity and Babinski signs. Intellectual development may be variably affected. Psychiatric symptoms, including personality changes with impulsivity, depression, and emotional lability, are common (Pellecchia et al., 2005). A specific brain MRI abnormality, the eye-of-the-tiger sign, is characteristic of the disease, with rare exceptions. Hypoprebetalipoproteinemia and acanthocytosis may be additional manifestations of PANK2 mutations. The diagnosis relies on clinical and MRI features. When both are consistent with PKAN, there is a high likelihood of identifying a pathogenic mutation in PANK2 by DNA sequencing, although large chromosomal deletions affecting one allele are likely to remain undetected by this method.

XII. Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome is a malformative autosomal recessive disorder caused by abnormal cholesterol metabolism resulting from deficiency of the enzyme 7-dehydrocholesterol reductase due to mutations of the DHCR7 gene located in chromosome 11. Decreased activity of 7-dehydrocholesterol reductase leads to a reduction in the rate of conversion of 7-dehydrocholesterol to cholesterol, causing an associated elevation in the serum concentration of 7-dehydrocholesterol or in the 7-dehydrocholesterol:cholesterol ratio (Opitz et al., 2002). A variety of proteins can be directly modulated by cholesterol, including the Sonic hedgehog and its related proteins Indian and Desert hedgehog, which require the covalent attachment of cholesterol to exert their morphogenetic function during development. Cholesterol is also an essential component of membranes and contributes to the formation of membrane lipid rafts, important for signaling. Patients manifest hypotonia and prenatal and postnatal growth retardation, microcephaly with intellectual deficiency and multiple malformations, including a characteristic facies (temporal narrowing, downslanting palpebral fissures, epicantthal folds, blepharoptosis, anteverted nares, cleft palate, and micrognathia), cardiac defects, underdeveloped external genitalia (hypospadias, bilateral cryptorchidism, and undermasculinization resulting in female external genitalia), postaxial polydactyly, and 2-3 toe syndactyly.

Holoprosencephaly can be an associated manifestation (Hennekam, 2005). Tandem mass spectrometry of dried blood card samples readily identifies patients and may be used for newborn screening. Direct analysis of the DHCR7 gene by DNA sequencing confirms the presence of a mutation in most cases. The combination of low concentrations of unconjugated estriol, HCG, and alphafetoprotein on routine maternal serum testing at 17 to 18 weeks’ gestation is also suggestive of maternal carrier status and thus places the fetus at risk for Smith-Lemli-Opitz syndrome. Measurement of 7-dehydrocholesterol levels in amniotic fluid is available for prenatal diagnosis. Treatment with cholesterol supplementation and bile acids improves growth. The addition of the HMG-CoA reductase inhibitor simvastatin helps reduce serum 7-dehydrocholesterol.

References

Metabolic Diseases of the Nervous System


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