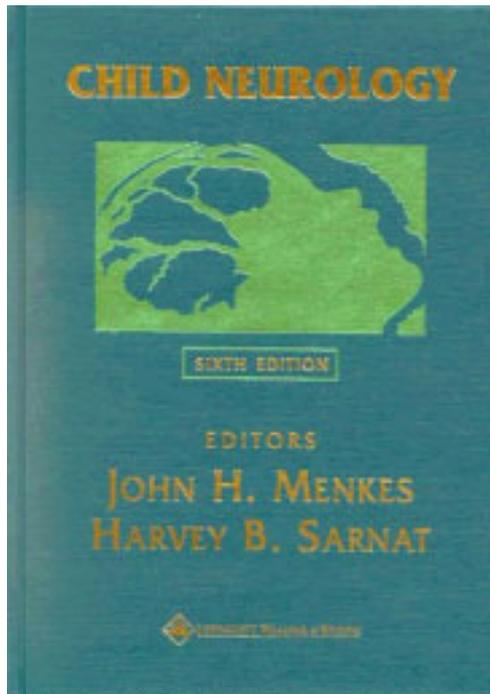

Child Neurology 6th edition (April 15, 2000): by John H. Menkes (Editor), Harvey B. Sarnat, Sam



By OkDoKeY

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To Joan, my wife, for giving me the pleasure of
and

To my teachers:

B.G.B.

(1901–1988)

S.S.G.

A.S.N.

S.C.

D.B.C.

(1913–1992)

—J.H.M.

To my wife, Laura

—H.B.S

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Preface to the Sixth Edition

A text such as this one, which strives to blend the neurosciences with clinical pediatric neurology, must be ready to render the increasing complexity of molecular biology, genetics, neurochemistry, and immunology readily apprehended by the clinician and lead him or her to understand how the innumerable developments affect the care, and treatment of patients.

My predecessors had an easier task. Frank R. Ford, under whose tutelage I had the good fortune to write the standard text of pediatric neurology, *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, inscribing my text, "Doctor, there are many things in here I don't know much about." Thomas Farmer wrote excellent textbooks of pediatric neurology, but these texts were also published decades ago, and none were both comprehensive and accurate. The one exception is Jean Aicardi's new text, *Diseases of the Nervous System in Childhood*, which defies the laws of gravity.

To obtain a broader point of view, I have therefore called on Harvey B. Sarnat and his expertise in neuroimmunology to assist me as coeditor of this edition. The list of authors has also been enlarged, with contributors in neuroimmunology, and neuro-oncology. As before, I have enlisted experts in pediatric cardiology, pediatric transplantation to help me with the chapter that deals with the neurologic manifestations of systemic diseases, and the chapter that deals with disorders of mental development. Theirs was an unenviable task.

Errors of omission and commission are inevitable in a text of this breadth and size. What will also be inevitable are the developments: a lag period of at least 1 year between completion of scientific work and its citation in a textbook. I have retained and sometimes even enlarged the number of classic citations. Too often, younger practitioners have replaced the pioneers in our field. We have taken care that these were not cast aside in the process of updating.

My thanks also go to William R. Wilcox and Andre Vanderhal of the Department of Pediatrics, Cedars-Sinai Medical Library for their assistance in preparing the new edition.

Preface to the First Edition

Even in a textbook, prefaces are written not to be read but rather to blunt inevitable criticisms. One of the first-rate pediatric neurology texts, was this book ever written. The main excuse for becoming involved in this already overwhelmed medical audience, is the hope of being able to offer a new viewpoint of the field. Pediatric neurology has felt the impact of the many recent advances in the neurosciences. Their magnitude has not yet been read. At that time, clinical descriptions achieved a degree of clarity and conciseness, which has not yet been equaled. Yet the reader who finds the explanation of Tay-Sachs disease^{*} offered during the last year, a great achievement at the great strides made during a relatively brief historical period. However, at the same time, what is accepted and taught today, will make as little sense fifty years hence.

It is the aim of this text to incorporate some of the knowledge derived from the basic neurologic sciences into the study of neurologic disease. Obviously, this can only be done to a limited extent. For some conditions the basic research and available experimental data only provide tangential information. Even when biochemical or physiologic details of their full presentation has been avoided, for to do so with any degree of completeness would require a text to go far beyond the intent of the text. The author and his colleagues have therefore chosen to review the basic impact, and to refer the reader to the literature for some of the remaining information. They have also included a brief examination of children. This subject is extremely well presented by R. S. Paine and T. E. Oppe, in their book. Anyone seriously interested in pediatric neurology should read.

In covering the field, extensive use of literature references has been made. These generally serve to:

- (1) A classic or early description of the condition.
- (2) Background information pertaining to the relevant neurologic sciences.
- (3) A current review of the condition.
- (4) In the case of some of the rarer clinical entities, the presentation of several key references was preferred.

It is hoped that this approach will serve to keep the text reasonably compact, yet allow it to be used as a reference.

^{*}Namely, "an inherited weakness of the central nervous system, especially of the ganglion cells, and a premature degeneration of the same."

^{**}London, Wm. Heinemann, 1966.

*[There was] . . . a time when theses in medicine could still be beautifully literary, since ignorance and
art.*

—Kurt Vonnegut, Jr.

Be kind to my mistakes, and live happy.

—Anonymous translator of *Robinson Crusoe* into Italian; c. 1719

Chapter 1

Metabolic Diseases of the Nervous System

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Evaluation of the Patient Suspected of Having a Metabolic Disorder

Metabolic Screening

Radiography

Serum Lysosomal Enzyme Screen

Structural and Biochemical Alterations

Disorders of Amino Acid Metabolism

Phenylketonuria

Tyrosinosis and Tyrosinemia

Maple Syrup Urine Disease

Nonketotic Hyperglycinemia

Defects in Urea Cycle Metabolism

Histidinemia

Defects in the Metabolism of Sulfur Amino Acids

Other Rare Metabolic Defects

Disorders of Amino Acid Transport

Hartnup Disease

Lowry Syndrome (Oculocerebrorenal Syndrome)

Disorders of Carbohydrate Metabolism

Galactosemia

Fructose Intolerance

Other Disorders of Carbohydrate Metabolism

Organic Acidurias

Propionic Acidemia (Ketotic Hyperglycinemia)

Methylmalonic Aciduria

Isovaleric Aciduria

Glutaric Acidurias

Disorders of Fatty Acid Oxidation

Disorders of Biotin Metabolism

Lysosomal Storage Diseases

Glycogen Storage Diseases (Glycogenoses)

Mucopolysaccharidoses

Mucopolysaccharidoses

Glycoproteinoses

Sphingolipidoses

Disorders of Lipid Metabolism

Cerebrotendinous Xanthomatosis

Smith-Lemli-Opitz Syndrome

Cholesterol Storage Diseases

Peroxisomal Disorders

Disorders of Peroxisomal Biogenesis

Single Peroxisomal Enzyme Defects

Defects of Multiple Peroxisomal Enzymes

Carbohydrate-Deficient Glycoprotein Syndromes

Familial Myoclonus Epilepsies

Lafora Disease

characteristic chemical abnormalities of tissues or body fluids.

Since 1975, almost all of the nearly 500 neurologic and neuromuscular diseases caused by known chromosome region, and a large proportion of them have been cloned (1). In the course of these a has become available, whose full discussion is outside the domain of this text. Rather, the emphasis their diagnosis and treatment, and, when known, the mechanisms that induce the neurologic deficit basis of the neurologic disorders, the reader is referred to a text by Rosenberg and coworkers (2).

Inborn errors of metabolism affect only approximately 1 in 5,000 live births and are therefore relatively importance rests in part on the insight they offer into the relationship between a genetic mutation, the nervous system.

The mechanisms by which inborn errors of metabolism produce brain dysfunction remain largely unknown pathogenesis has been proposed. Not all enzyme defects lead to disease; a large number of harmful original four inborn errors of metabolism described by Garrod (3), cystathioninuria, hydroxyproliner when inmates of institutions for the mentally retarded were screened for metabolic defects.

An introduction to the fundamentals of molecular genetics is far beyond the scope of this text. The colleagues (5) and Lewin (6).

For practical purposes, metabolic disorders are divided into the following groups:

- Disorders of amino acid metabolism
- Disorders of membrane transport
- Disorders of carbohydrate metabolism
- Organic acidurias
- Lysosomal storage diseases
- Disorders of lipid and lipoprotein metabolism
- Peroxisomal disorders
- Familial myoclonus epilepsies
- Ceroid lipofuscinosis and other lipidoses
- Disorders of metal metabolism
- Disorders of purine and pyrimidine metabolism
- Mitochondrial disorders

EVALUATION OF THE PATIENT SUSPECTED OF HAVING A METABOLIC DISORDER

The spectacular advances of molecular biology have facilitated the diagnosis and prevention of genetic therapy. The clinician must, therefore, strive for an early diagnosis of inborn errors of metabolism to counseling, and, in many instances, give parents an opportunity for an antenatal diagnosis on the

Since the initial descriptions of phenylketonuria and maple syrup urine disease, the protean clinical apparent. As a consequence, these disorders must be included in the differential diagnosis of neuro child medical history and physical examination.

Two questions should be considered: What type of patient is suspect for an inborn error of metabolism evaluation? It is clear that the greater the suspicion of a metabolic disorder, the more intense the in

Table 1.1 lists some clinical syndromes arranged according to decreasing likelihood of an underlying

When embarking on a metabolic investigation, procedures are performed in ascending order of cost.

Metabolic Screening

Routine screening of plasma and urine detects the overwhelming majority of disorders of amino acid metabolism and organic acids, as well as the common disorders of carbohydrate metabolism. At our institution, metabolic screening includes measurement of organic acids. The yield on these tests is low, and a high frequency of nonspecific or nondiagnostic results is observed. Elevated concentrations of blood ammonia with the patient in the fasting state or on a high-protein diet are characteristic of urea cycle disorders. Hypoglycemia or intermittent acidosis is characteristic of hypoglycemia or intermittent acidosis. Elevated lactic and pyruvic acid levels in serum are characteristic of mitochondrial disorders. Hence, determination of fasting blood sugar, serum pH, pCO₂, and lactic acid are essential when the suspicion for a metabolic disorder is high, these determinations should be repeated with the child in the fasting state. Other biochemical determinations required in the evaluation of a patient with a suspected metabolic disorder include measurement of serum carnitine levels (including total, acyl, and free carnitine), immunoglobulins, T₄, T₃, serum copper, and very long chain fatty acids diagnoses adrenoleukodystrophy and other peroxisomal disorders.

Radiography

Radiographic examination of the vertebrae and long bones can be used to diagnose most of the mucopolysaccharidoses and GM₁ gangliosidosis. Neuroimaging studies, including magnetic resonance imaging (MRI), have become increasingly important. Abnormalities such as agenesis of the corpus callosum and a large operculum seen in a few of the mucopolysaccharidoses are much higher when a child with mental retardation with or without seizures is subjected to MRI. As a rule, the computed tomographic (CT) scanning or MRI shows a significant abnormality in approximately 80% of cases (8). As a rule, MRI provides more information than CT. As is noted in [Chapter 2](#), in the Diseases with Mental Retardation, MRI is useful also in the diagnosis of the various leukodystrophies.

Serum Lysosomal Enzyme Screen

A serum lysosomal enzyme screen should be performed. In particular, assays for b-galactosidase, hexosaminidase, and the number of centers.

Structural and Biochemical Alterations

In a number of metabolic disorders, notably the lipidoses and white matter degenerations, diagnosis is established by ultrastructural, and biochemical studies on biopsied tissue. In the past, a brain biopsy was required for diagnosis. In many cases, structural and biochemical alterations can be detected outside the central nervous system (CNS) in peripheral tissues. Diseases (discussed in [Chapter 1](#) and [Chapter 2](#)) are likely to be diagnosed by examination of various tissues.

Tissue studied	Diseases
Peripheral nerve	Metachromatic leukodystrophy Globoid cell leukodystrophy Infantile neuroaxonal dystrophy Fabry disease Krabbe disease Tangier disease
Skin, conjunctiva, lymphocytes	Mucopolysaccharidoses, particularly the uronic acid and uronic acid sulfated Mucopolysaccharidoses Langer disease Neuroaxonal dystrophy* Mucopolysaccharidoses Sargliosis syndrome Fabry disease
Muscle	Late infantile and juvenile neuronal ceroid lipofuscinosis Fenilketonuria Mucopolysaccharidoses Mucopolysaccharidoses Nuclease-Pick disease Gaucher diseases
Brain marrow	Gaucher diseases All lipidoses, and degenerative diseases of gray matter All white matter degenerations, with the possible exception of Feline-Hurler disease None of the mucopolysaccharidoses, except Hurler disease
Brain	Gaucher diseases All lipidoses, and degenerative diseases of gray matter All white matter degenerations, with the possible exception of Feline-Hurler disease None of the mucopolysaccharidoses, except Hurler disease

*When storage is confined to nerve fibers (e.g., neuroaxonal dystrophy) conjunctival biopsy is not diagnostic.

TABLE 1.3. Common diseases diagnosed by study of tissues

GTP cyclohydrolase is seen also in dopa-responsive dystonia (see [Chapter 2](#)). [NADP⁺, nicotinamide-adenine dinucleotide phosphate (reduced form).]

PAH is normally found in liver, kidney, and pancreas, but not in brain or skin fibroblasts. The enzyme has a molecular weight of approximately 100,000. The gene coding for the enzyme has been cloned and the gene is approximately 90 kilobase (kb) long and codes for a mature RNA of approximately 2,400 base pairs. Analysis of patients with PKU and has confirmed that PKU is the consequence of numerous mutations. Over 100 mutations have been recorded, with the frequency of the mutations differing considerably between ethnic groups. The frequency of heterozygotes is greater than homozygotes in the precise meaning of the term ([12](#)). Some mutations result in little or no PAH activity, while others result in significant enzyme activity ([13,13a](#)). As a rule, the biochemical phenotype (i.e., the degree of phenylalanine in the blood) is predicted from the genetic mutation. In the experience of Ramus and colleagues, however, no good correlation exists between the degree of untreated patients, and a good likelihood exists that various environmental factors and modifying

Dihydropteridine reductase, a heat-stable enzyme involved in phenylalanine hydroxylation (see [Fig. 1.4](#)). It is present in normal amounts in classic PKU, but is absent or defective in one type of the non-

The infant with classic PKU is born with only slightly elevated phenylalanine blood levels, but because of the high protein content of food proteins and postnatal catabolism accumulates in serum and CSF and is excreted in large quantities. It is converted to phenylpyruvic acid, phenylacetic acid, and phenylacetylglutamine.

The transamination of phenylalanine to phenylpyruvic acid is sometimes deficient for the first few days of life. The onset of the defect is detected varies from 2 to 34 days. From the first week of life, o-hydroxyphenylacetic acid also is excreted in the urine.

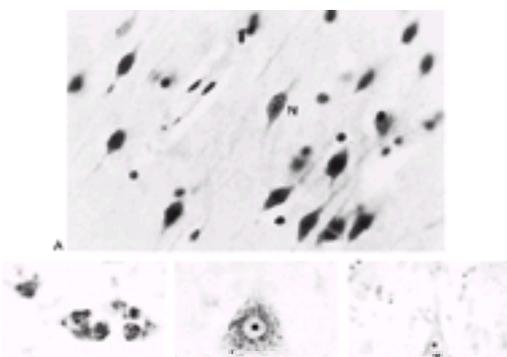
In addition to the disruption of phenylalanine metabolism, tryptophan and tyrosine are handled abnormally in PKU, and fecal content of tryptophan and tyrosine is increased. These abnormalities are reversed by treatment. Miyamoto and Fitzpatrick suggested that a similar interference might occur in the oxidation of tyrosine to melanin and might be responsible for the deficiency of hair and skin pigment in phenylketonuric individuals (10). This was extended by Scriver and colleagues ([11](#)).

Pathologic Anatomy

Alterations within the brain are nonspecific and diffuse. They involve gray and white matter, and the

Interference with the Normal Maturation of the Brain

Brain growth is reduced, and microscopic examination shows impaired cortical layering, delayed myelination. Additionally, the amount of Nissl granules is markedly deficient. This is particularly evident in those areas where the branching arborization and the number of synaptic spikes are reduced within the cortex ([17](#)). These changes occur during the last trimester of gestation into postnatal life ([Fig. 1.2](#)).



Diminished or Absent Pigmentation of the Substantia Nigra and Locus Ceruleus

Because substantia nigra and locus ceruleus are normally pigmented in albinos, and tyrosinase activity in the substantia nigra, diminished or absent pigmentation is not a result of tyrosinase inhibition by phenylalanine. In a phenylketonuric patient must be interrupted at some other metabolic point, such as the metal-catalyzed conversion of lipofuscin to melanin, which is responsible for the melanization of lipofuscin in the substantia nigra (19).

Clinical Manifestations

Phenylketonuric infants appear healthy at birth. In untreated infants, vomiting, which at times is profuse, is common. By 49 months, delayed intellectual development becomes apparent (20). In the untreated classic case, intellectual development is severely retarded. Children in this category have an IQ below 50. Seizures, common in the more severely retarded, occur spontaneously. During infancy, they often take the form of infantile spasms, later changing into tonic-clonic seizures.

The untreated phenylketonuric child is blond and blue-eyed, with normal and often pleasant features. A musty odor, attributable to phenylacetic acid, can suggest the diagnosis. Significant neurologic abnormalities are not unusual. Microcephaly may be present, as well as a mild increase in muscle tone, particularly in the lower extremities. A hand sign is seen in approximately 30% of the subjects. Parkinsonianlike extrapyramidal symptoms also occur. The extensor digitorum is the most commonly affected muscle.

A variety of electroencephalographic (EEG) abnormalities has been found, but hypsarrhythmic pattern is the most common. Multiple foci of spike and polyspike discharges are the most common (22). Neurologic examination is abnormal in 40% in the experience of Thompson and colleagues (23). Abnormalities included hyperactive reflexes, rigidity, and abnormal eye movements.

MRI is abnormal in almost every subject, regardless of when treatment was initiated. On T2-weighted images, increased signal in the subcortical white matter of the posterior hemispheres. Increased signal can extend to involve the deep white matter of the anterior hemispheres. No signal abnormalities are seen in brainstem, cerebellum, or cortex, although cortical atrophy is seen. This abnormality is unrelated to the subject's IQ, but is significantly associated with the phenylalanine level. After 10 years off their diets, resumption of dietary treatment can improve MRI abnormalities within a few weeks. The MRI changes are the result of edema (23,25).

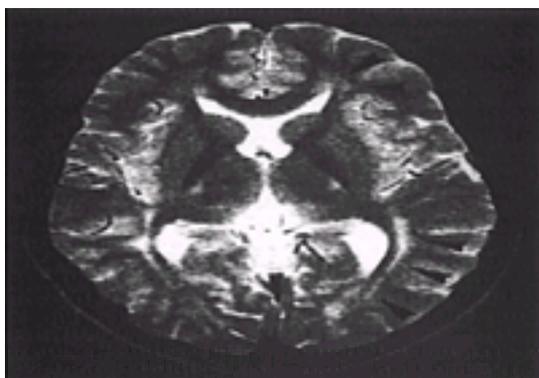


FIG. 1.4. T2-weighted magnetic resonance imaging of a 16-year-old girl with phenylketonuria. The scan was performed at 16 years of age. At the time of the scan, her neurologic examination was normal, but her phenylalanine level was high. The MRI shows high signal, particularly in the parieto-occipital areas, but also at the tips of the anterior horns of the lateral ventricles. (From the Neurorehabilitation Section, Institute of Neurology, University of London.)

Heterozygous mothers tend to have elevated plasma phenylalanine levels and somewhat reduced intelligence. Mothers of offspring with PKU have a higher incidence of mental retardation. A deficiency

phenotypes are the result of different phenotypic severity of the various mutations in the PAH gene compound heterozygotes for a mutation that abolishes catalytic activity of PAH, and one that reduces levels range between 4 and 20 mg/dL (242 and 1,212 $\mu\text{mol/L}$), and the majority appear to have uni

In infants with mild hyperphenylalaninemia, the increase in blood phenylalanine is sufficiently slow performed at 72 hours. When follow-up phenylalanine determinations are run between ages 2 and milder hyperphenylalaninemias and in patients with PKU whose initial screening test result was rep of patients with PKU who missed being diagnosed by screening during the neonatal period (approx responsible for 58% of the missed cases and inadequate follow-up for 21% (43). Approximately on

Genotypically, prenatal determination of the heterozygote or homozygote can be performed by gen polymorphisms derived from DNA extracted from lymphocytes. Radiolabeled nucleotides specific fo polymerase chain reaction technique using DNA isolated from lymphocytes of classic patients with *in vitro*, so that considerable quantities become available and can be used by hybridization studies in the DNA of a given subject (Fig. 1.5) (44,45).

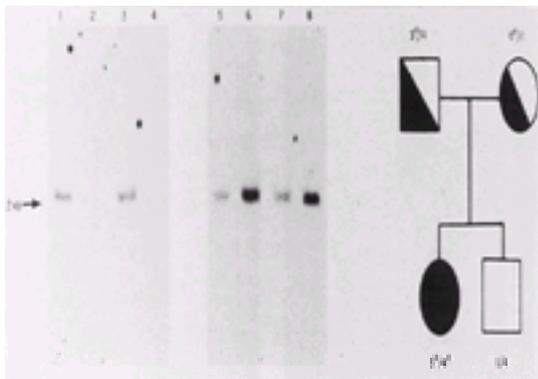


FIG. 1.5. Oligonucleotide hybridization analysis. Lanes 1 and 5, father; lanes 2 and 6, mother; lane unaffected child. A mutant splicing probe specific for the exon/intron 12 splice junction was used for used for lanes 5 to 8. DNA was isolated from leukocytes of family members, digested with the restr segregation of PKU alleles (*) and the restriction fraction polymorphism haplotypes for each family mutant haplotype 3 gene that hybridizes to the mutant splicing probe (lane 1), and a normal haplotype. The mother has a mutant haplotype 4 gene and a normal haplotype 1 gene. The mutant splicing probe hybridizes strongly (lane 6). The data show that the PKU mutation associated with the associated with the father's mutant haplotype 3 allele. The PKU child in this family inherited the mutant gene from his mother. DNA isolated from this child hybridized to both the mutant and the normal splicing probe, indicating that the child is a compound heterozygote. The child inherited the mutant gene from his father and the normal haplotype 1 allele from his mother. He hybridizes strongly to the normal probe, and the other mutant was not available. (From DiLella AG, Woo SL. Molecular basis of phenylketonuria. permission.)

Other Conditions Characterized by Hyperphenylalaninemia

Three forms of phenylalaninemia, accounting for 13% of cases of elevated phenylalanine levels in v and many neurologic deficits, are aptly termed *malignant phenylalaninemia*. Biochemically, these conditions are characterized by a deficiency of tetrahydrobiopterin (BH_4), the cofactor in the hydroxylation of phenylalanine to tyrosine.

The first and most common of these conditions to be recognized is characterized by undetectable or very low levels of tetrahydrobiopterin in fibroblasts, but normal hepatic PAH activity (46). Dihydropteridine reductase is responsible for the conversion of dihydrobiopterin to tetrahydrobiopterin (see Fig. 1.1). BH_4 levels are low in blood, urine, CSF, and a number of tissues. Because BH_4 is a

on a low-phenylalanine diet immediately. Infants whose blood phenylalanine concentrations remain treated also.

The generally accepted therapy for classic PKU is restriction of the dietary intake of phenylalanine. The diet should be managed by a team consisting of a nutritionist, a physician with expertise in metabolism. To avoid symptoms of phenylalanine deficiency, milk is added to the diet in amounts sufficient to maintain levels between 120 and 360 μmol/L. Generally, patients tolerate this diet quite well, and within 1 to 2 weeks, the serum phenylalanine determinations are essential to ensure adequate regulation of diet. These are performed monthly thereafter.

Strict dietary control should be maintained for as long as possible, and most centers strive to keep patients in the moderate and mild PKU range. Samples of low-phenylalanine menus are given by Buist and colleagues (59). Dietary lapses frequently are accompanied by behavioral problems. Dietitians and dietetic workers have suggested supplementation of the low-phenylalanine diet with tyrosine, but no statistically significant outcome. Failure to treat subjects with mild hyperphenylalaninemia does not appear to produce either mental retardation or epilepsy.

Dietary therapy has for the greater part been effective in preventing mental retardation in patients with classic PKU on several factors. Most important is the age at which the diet was initiated. Smith and coworkers found that the longer the interval between birth and start of treatment (61). The average phenylalanine concentration while receiving the diet in the most recent cohorts being 5.0 to 6.6 mg/dL (300 to 400 μmol/L). Additionally, the length of time that phenylalanine concentration was below 2.0 mg/dL (120 μmol/L), also affected outcome. The most favorable diagnostic and treatment characteristics have lower IQs than other members of the cohort, and behavioral problems, notably hyperactivity (61,62 and 63). Dietary supplementation with tyrosine does not improve performance on neuropsychological tests (64). The most likely explanations for these deficiencies are the effects of elevated phenylalanine on the developing brain with induction of minor structural malformations.

When patients who already have developed symptoms caused by classic PKU are placed on the diet and maintained, their EEG results tend to revert to normal. Microcephaly, if present, can correct itself, and abnormal growth curves return to normal.

Considerable uncertainty exists about when, if ever, to terminate the diet (65). In the series of Waisbren, patients discontinued at 5 years of age had a reduction in IQ of 10 points or more during the ensuing 5 years. The length of restrictive diet predicted the change in IQ. Of the children whose IQs dropped 20 or more points, 90% were below 70, and 40% of those whose IQs rose 10 points or more had a phenylalanine level of less than 2.0 mg/dL. Discontinuation of the diet was accompanied by the evolution of spasticity and worsening of white matter abnormalities. Reports such as these indicate that dietary therapy for patients with classical PKU should be lifelong.

The inadequacies of dietary therapy underline the need for a more definitive approach to the treatment of inborn errors of metabolism. Gene therapy is being used for the treatment of a variety of genetic diseases (Table 1.4). The likelihood that this approach will be successful depends on the tissue-specific expression of the normal gene product, the patient's clinical symptoms, and the site of the defective enzyme. Since the defective enzyme is not normally expressed in bone marrow-derived cells, and bone marrow transplantation for the treatment of inborn errors of metabolism affecting the nervous system has been successful in Crigler-Najjar disease, and tyrosinemia type I (71).

Disease	Expression	Results of treatment
Chédiak-Higashi syndrome	Expression of genetic defect restricted to lymphoid and hematopoietic cells	Correctable by BMT
Gaucher disease (adult form)	Generalized genetic defect; symptoms restricted to lymphohematopoietic cells	Correctable by BMT
Adrenoleukodystrophy	Generalized genetic defect; generalized clinical symptoms with central nervous system involvement	May be correctable by BMT
Metachromatic leukodystrophy	—	Adult form may be stabilized
Central retinodystrophy	—	—
Mucopolysaccharidosis	—	—
Hurler disease	—	Visceral symptoms improve; neurologic symptoms may stabilize
Hunter disease	—	Visceral symptoms improve; neurologic symptoms appear to progress
Santalo disease	—	No effect of neurologic symptoms
Phenylketonuria	Lymphohematopoietic cells do not express normal gene product	Not correctable by BMT

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is a familial cerebral degenerative disease caused by a defect in the passage of urine that has a sweet, maple syrup–like odor. It was first described in 1954 by Menkes, and is now diagnosed throughout the world, and its incidence is estimated at 1 in 220,000 births (76). In some populations, however, is as high as 1 in 176 births (77). The disease occurs in all races and is transmitted in an

Molecular Genetics and Biochemical Pathology

MSUD is characterized by the accumulation of three branched chain ketoacids: α -ketoisocaproic acid, α -ketovaleric acid, and α -ketoisovaleric acid, derivatives of leucine, valine, and isoleucine, respectively (78,79). Their accumulation is the consequence of a defect in the degradation of these ketoacids (Fig. 1.6).



FIG. 1.6. Degradation of leucine in mammalian tissues. In maple syrup urine disease, the metabolic pathway is confined to step 3. A rare entity with a possible metabolic block at step 4 also has been reported.

The branched chain α -ketoacid dehydrogenase complex is located within the mitochondrial inner membrane and comprises six proteins: E_{1a} and E_{1b} , which form the decarboxylase; E_2 ; E_3 ; and a branched chain α -ketoacid dehydrogenase. The activity of the complex is regulated by phosphorylating and dephosphorylating the dehydrogenase. E_1 is a thiol-dependent enzyme that acts as a dihydrolipoyltransferase, transfers the acyl group from the first enzyme to coenzyme A. The third enzyme, E_3 , reoxidizes the disulfhydryl form of lipoamide. The same enzyme is common to other α -ketoacid dehydrogenase complexes (80). The complex removes carboxyl groups from all three branched chain ketoacid derivatives (see Fig. 1.6, step 2).

With six genes involved in the function of the branched chain ketoacid dehydrogenase complex, copies of the genes for E_{1a} , E_{1b} , E_2 , and E_3 have been described, with many MSUD patients being compound heterozygotes. The range of clinical severity from the severe, classic form of MSUD to mild and intermittent forms.

As a consequence of the enzymatic defect, the branched chain ketoacids accumulate in serum and urine. In addition, levels of the respective amino acids (e.g., leucine, isoleucine, and valine) are elevated secondary to the defect. α -keto-b-methylvaleric acid, also has been found in serum (81). In some patients, α -hydroxyisovaleric acid (82), are excreted also. Sotolone, a derivative of α -ketobutyric acid, the decarboxylated form of α -keto-b-methylvaleric acid, is responsible for the characteristic odor of the patient's urine and perspiration.

Pathologic Anatomy

Structural alterations in the nervous system in untreated infants with MSUD are similar to those seen in other organic acidurias, but more

organic acidemias.

Diagnosis

Clinically, MSUD is diagnosed by the characteristic odor of the patient and by a positive 2,4-dinitrophenylhydrazine test. Plasma amino acids are elevated by the time the infant is 24 hours old, even in those infants who have not yet been given a bacterial inhibition assay analogous to that used for the neonatal diagnosis of PKU is performed in the laboratory (100). Tandem mass spectroscopy also can be used and has the advantage of obtaining rapid quantitative results (36a). The presence of the branched chain ketoacid decarboxylases in cultivated amniocytes and chorionic villi is detectable as early as 10 weeks' gestation (101).

Treatment

Treatment consists of restricting the dietary intake of the branched chain amino acids through the use of a special formula. For optimal results, infants should be placed on the diet during the first few days of life and should receive prompt and vigorous treatment of even mild infections is mandatory; a number of children on this synthetic diet have died.

Peritoneal dialysis or multiple exchange transfusions have been used to correct coma or other acute complications. Another, simpler approach is to provide intravenously or by nasogastric tube an amino acid mixture that is deficient in branched chain amino acids. In children in whom long-term dietary therapy was initiated during the first 2 weeks of life, and whose intelligence quotients are nearly normal IQs (104). In the experience of Hilliges and coworkers, the mean IQ of MSUD patients is similar to that for early treated patients with PKU. The length of time after birth that plasma leucine concentrations are elevated, of residual branched chain ketoacid dehydrogenase activity (105). The thiamin-responsive cholestanoluria is a

Nonketotic Hyperglycinemia

This relatively common family of diseases is marked by genetic and phenotypic heterogeneity, and by a wide range of symptoms (118). In the infantile form, neurologic symptoms begin during the neonatal period. They include myoclonic seizures, apnea, and progressive obtundation with coma and respiratory arrest. The EEG shows a characteristic hypsarrhythmia (119). Nystagmus and a marked depression of the electroretinogram results (ERG) are also seen. In the neonatal period; those who survive are profoundly retarded. A transient neonatal form has been reported, and a permanent form of nonketotic hyperglycinemia. However, symptoms remit abruptly after a few days.

A less severe form becomes apparent during the latter part of the first year of life after several months of normal development, leading to decerebrate rigidity. Extrapyramidal signs are not uncommon (121). A juvenile form with a more insidious onset has been reported, as has a neurodegenerative picture (119,122).

Pathologic examination of the brain in the infantile form of the disease discloses a reduction in white matter and a marked gliosis (122). Partial or complete agenesis of the corpus callosum has been described, and a

The marked increase in plasma and CSF glycine, and the markedly elevated ratio of CSF glycine to creatinine, and the absence of shows decreased or absent supratentorial white matter, with thinning of the corpus callosum and

The basic defect in this condition is localized to the mitochondrial glycine cleavage system, which is a complex reaction requires four protein components and, to date, defects in one or another of three genes have been identified. A correlation exists between the clinical expression of the disease and the genetic lesion. The classic form is associated with the absence of the pyridoxal-containing decarboxylase (P protein), and the milder atypical forms with

The pathophysiology of the neurologic abnormalities has not been established fully. Glycine is an inhibitory neurotransmitter in the brainstem levels. It also acts as a coagonist for the *N*-methyl-D-aspartate glutamate receptor, modulating its activity through a mechanism (119). The inhibitory effects of glycine are blocked by strychnine, but its effectiveness on the *N*-methyl-D-aspartate receptor, such as dextromorphan or ketamine, may have beneficial effects in the treatment of these conditions. Their accurate assessment (125,126).

Argininosuccinic Aciduria

Argininosuccinic aciduria is one of the more common of the urea cycle disorders. The condition is characterized by the accumulation of argininosuccinic acid in body fluids. It was first described in 1958 by Allan and others.

Molecular Genetics and Biochemical Pathology

Argininosuccinic acid is a normal intermediary metabolite in the synthesis of urea (see [Fig. 1.7](#)). A gene on chromosome 7, has been demonstrated in liver and skin fibroblast cultures ([132](#)).

The synthesis of urea is only slightly depressed, but a large proportion of labeled ammonium lactate is converted to urea ([133](#)). The manner in which children synthesize urea is not clear. It appears likely that in argininosuccinic aciduria the substrate accumulates to a concentration at which the decreased substrate-binding capacity of the enzyme results in levels greater than the K_m for the mutated enzyme ([134](#)).

Pathologic Anatomy

The liver architecture is abnormal, with increased fat deposition. The brain in one patient who died had extensive white matter. The cortical layers were poorly developed, and myelination was defective with vacuolation. An older patient had atypical astrocytes similar to the Alzheimer II cells seen in Wilson disease and in some cases of argininosuccinic aciduria.

Clinical Manifestations

As ascertained by newborn screening, the incidence of argininosuccinic aciduria in Massachusetts is 1 in 10,000. Several clinical forms have been recognized, each resulting from a different genetic mutation ([138](#)).

The most severe entity is the neonatal form. Infants feed poorly, become lethargic, develop seizures, and die. In the milder forms, progression is less rapid, but similar symptoms appear in early infancy. In the majority of patients, the presenting symptoms are mental retardation, recurrent generalized convulsions, poorly pigmented skin, and growth retardation. Some patients have been seizure free, however, and have presented with little more than learning disability. Some have had normal intelligence without treatment ([141](#)).

Diagnosis

The presence of elevated blood ammonia should suggest a disorder in the urea cycle. Initial evaluation should include plasma lactate levels, liver function tests, quantitative assay of plasma amino acids, and assay of urea. The diagnosis of argininosuccinic aciduria can be made by a significant elevation of plasma citrulline, and the presence of argininosuccinic acid. In some instances, fasting blood ammonia level can be normal or only slightly elevated. Increased excretion of orotic acid is seen in all urea cycle defects, with the exception of CPS deficiency.

Treatment

Hyperammonemic coma in the neonate caused by any of the urea cycle defects requires prompt removal of the excess ammonia, and reduction in the formation of ammonia. Quantitative amino acid analysis and the infant should be given a high dose of intravenous glucose with insulin to suppress protein catabolism. Hemodialysis if available, or by peritoneal dialysis ([143](#)). Details of treatment are presented by Bruening. Treatment for increased intracranial pressure, which frequently accompanies neonatal hyperammonemia, is discussed in the section on hyperammonemia.

The long-term management of an infant who suffers a urea cycle defect is directed toward lowering ammonia as far as possible. This is accomplished by providing the infant with alternative pathways for waste nitrogen removal. The infant is placed on a protein-restricted diet (1.2 to 2.0 g/kg per day), which is supplemented with L-arginine and argininosuccinate as waste nitrogen products, and citrate, which improves weight gain and reduces ammonia levels.

urine amino acids. The disease was first reported in 1962 by Russell and coworkers (153) and is the enzyme has been cloned and localized to the short arm of the X chromosome (Xp21.1), close to the have been recorded, and most families have their own unique mutation (154). The enzyme defect in male subjects, it can be partial (155). As a consequence, blood ammonia levels are strikingly and contrasted with normal values of less than 0.1 mg/dL or 50 μmol/L), and CSF ammonia is at least 100 μmol/L; glutamate, and alanine; a striking reduction in plasma citrulline; and an increased excretion of orotic acid and carbamyl phosphate from mitochondria into cytosol, where it is converted into orotic acid (156).

As is the case in argininosuccinic aciduria, the neuropathologic picture is highlighted by the presence of hepatic encephalopathy, a striking degree of neuronal necrosis also exists. Electron microscopic examination of mitochondria (158).

As a rule, the magnitude of the enzymatic defect correlates with the severity of clinical symptoms. In severe cases, hyperammonemia. When the condition presents during the neonatal period it is rapidly progressive. Symptoms usually are delayed until the second day of life and are highlighted by feeding difficulties. Blood ammonia is at least five times normal, thus distinguishing the condition from sepsis (158a).

Less severe cases present with failure to thrive and with episodic attacks of headache and vomiting, which are often the consequence of protein ingestion and are accompanied by high blood ammonia levels (159). A considerable proportion of the neurologic symptoms, alterations in neurotransmitters, notably quinolinic acid, and increased tryptophan transport across the blood–brain barrier, also could be involved (128).

The disease is expressed more variably in the heterozygous female subject, with manifestations ranging from mild to severe. In symptomatic female subjects, behavioral abnormalities are almost invariable. In the series of Roach and colleagues, hyperactivity were seen in every patient. Episodic vomiting and lethargy were also invariable. Amino aciduria is present in 38%, and developmental delay in 35%. Seizures, generalized or focal, were seen in 23% (156). The disease is consistently when girls were symptomatic. Other girls are asymptomatic except for an aversion to protein. Valproate therapy can induce fatal hepatotoxicity in male subjects with OTC deficiency, and in heterozygous female subjects (160).

Treatment of OTC deficiency in the male or female subject is similar to treatment for argininosuccinic aciduria: a low-protein diet and increasing waste nitrogen excretion by the addition of sodium phenylbutyrate and sodium citrate. In infants at risk for neonatal OTC deficiency has been attempted with some success in that such infants have to be rescued from hyperammonemic coma (163). Orthoptic liver transplantation presents and the likelihood exists of surgical complications (164).

In some hemizygous male subjects, OTC deficiency is not complete, and the clinical course is not always followed by progressive cerebral degeneration or by the acute onset of cerebral and hepatic symptoms.

Ornithine transcarbamylase is expressed only in liver and in the small intestine; prenatal diagnosis by DNA analysis represent new mutations, this technique is of limited use, except for offspring of obligate gene carriers. In the diagnosis of heterozygotes by linkage analysis with restriction fragment polymorphisms in or around the gene, one can be asymptomatic or severely affected (155).

Carbamyl Phosphate Synthetase Deficiency

Carbamyl phosphate synthetase deficiency is a disorder of the urea cycle manifested by a reduction in blood ammonia. The condition was reported first by Freeman and associates (168).

Symptoms of CPS deficiency are the most severe of any of the urea cycle defects, and the neonatal course of the enzyme, is usually fatal. In partial CPS deficiency, symptoms appear in infancy and consist of hypotonia or hypertonia, and irregular eye movements. Autopsy reveals ulegyria of cerebral and cerebellar cortex and the central part of the brainstem. In contrast to argininosuccinic aciduria, no Alzheimer cells are seen. CPS deficiency is usually rapidly fatal (157,169).

across the inner mitochondrial membrane, possibly because of an abnormality of the transport prot

The other condition is ornithine-ketoacid aminotransferase deficiency. In this entity, ornithinemia is to night blindness. Intelligence is preserved, and no neurologic or muscular symptoms occur, although allelic variants have been described. In some of these, ornithinemia is corrected by treatment with a low-arginine diet (178).

Transient hyperammonemia with consequent profound neurologic depression can be encountered differentiated not only from the various urea cycle defects, but also from the various organic acidemias which can induce hyperammonemia (181). In these conditions, the accumulation of organic acids in the mitochondrial CPS, and the activities of all five enzymes of the urea cycle are depressed. On a clinical level, urea cycle defects in that infants with a urea cycle defect are asymptomatic for the first 24 hours of life, demonstrate tachypnea rather than a respiratory distress syndrome. In contrast to the distressed neonates, organic acidemias demonstrate ketonuria or ketonemia (182). Asymptomatic hyperammonemia is relatively common (183).

Histidinemia

Histidinemia is a harmless metabolic variant that is caused by a defect in histidase, the enzyme that converts histidine to glutamate. In this condition, plasma histidine levels and an excretion of large amounts of the amino acid occur (184).

Two other rare defects of histidine metabolism, urocanic aciduria and formiminotransferase deficiency, are also mentioned.

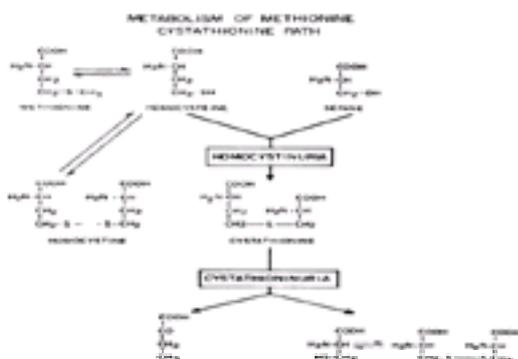
Defects in the Metabolism of Sulfur Amino Acids

Homocystinuria

The increased excretion of homocystine is a manifestation of several inborn errors of methionine metabolism. The most common is homocystinuria, which is associated with thromboembolic episodes, ectopia lentis, and mental retardation. Although discovered as late as 1932 (185), the prevalence of homocystinuria varies considerably from one country to another, ranging from 1 in 100,000 to 1 in 10,000 (186). The condition is transmitted by an autosomal recessive gene, localized to the long arm of chromosome 11.

Molecular Genetics and Biochemical Pathology

In the most common genetic form of homocystinuria, the metabolic defect affects cystathionine synthase, the enzyme that converts homocysteine and serine to cystathionine (Fig. 1.8) (187). The enzyme as purified from human liver has two isoforms, one in the cytosol and one in the mitochondria. The cytosolic form also has been found in brain and skin fibroblasts (189). Considerable genetic heterogeneity exists in the enzyme defect. In the majority, the lesion resides in a structural gene for the enzyme (190). In most homocystinuric subjects, the defect is a structural one, but rather interferes with its activation by pyridoxine (191). As a result, enzyme activity is low. In a proportion of affected families (approximately 25% to 50% of patients with homocystinuria), residual enzyme activity stimulates enzyme activity and partially or completely abolishes the excretion of homocystine, the condition is mild. These patients tend to have a milder phenotype of the disease.



Welch and Loscalzo (197). It also has become evident that an increased plasma homocysteine correlates with cardiovascular disease.

Clinical Manifestations

The pyridoxine-unresponsive form of homocystinuria is more severe in its manifestations than the pyridoxine-responsive form.

Homocystinuric infants appear healthy at birth, and their early development is unremarkable until symptoms occur between 5 and 9 months of age. Ectopia lentis is seen in more than 90% of affected individuals within the first 6 months, but it generally occurs between 3 and 10 years of age. The typical older homocystinuric child has characteristic skin blotches are seen over the skin, particularly across the maxillary areas and cheeks. The gait is shuffling and is present in most instances. Secondary glaucoma and cataracts are common (198).

In approximately 50% of the patients reported, major thromboembolic episodes have occurred on the pulmonary artery, coronary arteries, and renal artery and vein. Multiple major cerebrovascular accidents are common and closely resembles pseudobulbar palsy. Thromboembolic events are particularly common after even minor trauma. Cerebral thrombi are the cause of the mental retardation that occurs in 50% of the patients (199,200). In a large proportion of subjects, electromyography suggests myopathy (200).

Radiography reveals a biconcavity of the posterior aspects of the vertebrae (codfish vertebrae) (201) from childhood. Abnormalities of the hands and feet are noted also. These include metaphyseal spicules and delayed development of the lunate bone (202).

Diagnosis

The diagnosis of homocystinuria suggested by the appearance of the patient can be confirmed by the presence of methionine and homocystine, and by a positive urinary cyanide-nitroprusside reaction. Enzyme activity is measured in urine specimens.

Although ectopia lentis, arachnodactyly, and cardiovascular symptoms are seen also in Marfan syndrome, which is inherited by recessive transmission (in contrast to the dominant transmission of Marfan syndrome), the thromboembolic events, biconcave vertebrae, and the peculiar facial appearance (203). The relatively long fingers seen in Marfan syndrome remains constant. In homocystinuria, the skeleton is normal for the first few years of life, but the limb abnormalities develop. In homocystinuria, but also as an isolated congenital defect in the Weill-Marchesani syndrome and in some cases in conjunction with profound mental retardation, seizures commencing shortly after birth, acute hemiparesis, and other cases are the result of a deficiency of the molybdenum cofactor rather than of the apoenzyme, this is a defect of metal metabolism.

Cystathionine synthase has been found in cultivated amniotic fluid cells, and the condition, therefore, is not a defect of the enzyme.

Treatment

Restriction of methionine intake lowers plasma methionine and eliminates the abnormally high urinary excretion of methionine free and are supplemented by carbohydrates, fats, and fat-soluble vitamins generally low in methionine. They are supplemented with cystine.

Other dietary measures include the addition of folic acid, based on the assumption that the mental retardation in some coworkers have recommended treatment with betaine hydrochloride in subjects who do not respond to the diet.

In pyridoxine-responsive patients, large doses of the vitamin (250 to 1,200 mg/day) reduce or eliminate the neurological symptoms. The use of antiplatelet agents, such as aspirin or dipyridamole, has not yet been proven.

Early therapy appears to improve the ultimate IQ and delays the onset of thromboembolic episodes.

Hyperlysinemias

Several inborn errors are marked by an elevation in blood lysine levels and by increased urinary excretion of lysine.

Hyperlysinemia and saccharopinuria were first observed in patients with mental retardation and sei- zures in infancy. In these patients, as is the case for the iminoacidemias, the neurologic abnormalities have turned out to be due to hyperdibasic aminoaciduria. This condition is marked by abnormally high excretion of the dibasic amino acids in the urine, above normal plasma levels and a normal cystine excretion (214).

Increased excretion of lysine and arginine accompanied by hyperammonemia also is seen in families. Two types have been recognized, which are probably not allelic. In type I, the presenting symptoms include mental retardation, hyperammonemia or protein intolerance (214,215). Type II is not uncommon in Finland, where its inheritance is autosomal recessive (215). It manifests with protein intolerance, bouts of hyperammonemia, and mental retardation. The gene is located on chromosome 14 (14q11.2). The defective gene is believed to code for one of several permeases (216,216a).

Another disorder of lysine metabolism is pipecolatemia. This entity is identical with Zellweger cerebrotendinous lipoidosis, a Peroxisomal Disorder, later in this chapter.

The diagnosis of the various hyperlysinemias rests on the increased serum levels of lysine. High urinary excretion but with normal blood levels of both amino acids, also is seen in some heterozygotes for the hyperlysinemias.

Two other defects of lysine metabolism involve the conversion of α -aminoadipic acid to glutacoyl-CoA. In one retarded youngster and his apparently healthy brother, the defect is in the conversion of α -aminoadipic acid to glutacoyl-CoA. In another observed in a mentally retarded child, the defect is in the conversion of α -ketoadipic acid to glutaryl-CoA. These defects represent benign metabolic variants or truly have the potential of inducing neurologic symptoms. In the latter case, receiving vigabatrin for their seizures (220).

Other Rare Metabolic Defects

A few other extremely rare defects of amino acid metabolism associated with neurologic symptoms should be mentioned. In addition to the iminoacidemias, cystathioninuria, and histidinemia should caution the reader against accepting the number of neurologic disorders that are accompanied by aminoaciduria are not included in Table 1.6. In children who are screened, a few exhibit pathologic aminoaciduria. Deficiency diseases, notably rickets, and side effects of anticonvulsant therapy, can account for some of these; the remainder are unexplained.

Disease (reference)	Enzymatic defect	Clinical features	Diagnosis
Hyperlysinemia (214)	Ureidase deficiency	Weakness, failure to thrive, malnutrition, mental retardation	Increased blood and urine lysine; no increased excretion of lysine
Hyper- β -alaninemia (215)	β -Alanine-oxalo-glutarate transaminase	Seizures, convulsions, at birth, convulsions	Plasma urine β -alanine and β -oxalo-glutarate and elevated urinary β -alanine and oxalo-glutarate
Carnitine (216)	Carnitine	Seizures, mental retardation, malnutrition, muscular wasting, ataxia	Increased blood and urine carnitine; increased CSF carnitine
α -Methylcrotonyl-coenzyme A (216a)	α -Methylcrotonyl-coenzyme A	Ataxia, spastic, mental retardation, polydactyly, skin rash, convulsions	α -Methylcrotonyl and α -methyl- β -ketoglutaric acid in urine
Hyperphenylalaninemia (217)	Phenylalanine hydroxylase	Ataxia, spastic, mental retardation, polydactyly, skin rash, convulsions	Elevated urine β -alanine, oxalo-glutarate, and carnitine
Acetylglutamate synthase (218)	Acetylglutamate synthase	Progressive mental retardation, convulsions, ataxia, changes in behavior, changes in tubular function, ataxia, polydactyly, mental waste insufficiency	Elevated urine β -alanine, oxalo-glutarate, and carnitine
Cystathioninuria (219)	Deficiency of ACSF-cystathionin synthase	Mental retardation, convulsions, ataxia, polydactyly, skin rash, convulsions	Accumulation of glutathionyl-phenylalanine in urine and kidney
Cystathioninuria (219)	α -Cystathionin synthase	Mental retardation, convulsions, ataxia, polydactyly, skin rash, convulsions	Reduced cystathionin, glutathionin, increased aminoacids
Phenylketonuria (220)	Type I: phenylalanine hydroxylase; Type II: tetrahydrobiopterin deficiency	Progressive mental retardation, convulsions, ataxia, polydactyly, skin rash, convulsions	Increased urinary methyl acid with glyoxylic acid type I or α -glyoxylic acid

TABLE 1.6. Some rarely encountered defects of amino acid metabolism associated with neurologic symptoms.

No pathologic studies have yet been reported in typical patients with Hartnup disease.

Clinical Manifestations

The incidence of the biochemical lesion responsible for Hartnup disease is 1 in 18,000 in Massachusetts and Australia (241). Clinical manifestations of Hartnup disease are the consequence of several factors. Beriberi, acid levels, and symptoms are seen only in subjects with the lowest amino acid concentrations. Beriberi disease itself, as distinguished from its biochemical defect, is seen mainly in malnourished children. Neurologic and dermatologic signs appear (241). Also, no difference exists in rate of growth or IQ scores between Hartnup patients and coworkers, 90% of Hartnup subjects had normal development (242). However, low academic achievement in patients with Hartnup disease who, for genetic reasons, tended to have the lowest plasma amino acid concentrations.

When present, symptoms are intermittent and variable, and tend to improve with increasing age. A characteristic rash appears on the face, neck, and extensor surfaces of the extremities. This rash resembles the dermatitis of pellagra. Neurologic symptoms precede the rash for several years. They include intermittent personality changes, psychoses, migraines, and ataxia. Changes in hair texture also have been observed. The four children of the original Hartnup family had normal renal and intestinal transport is impaired in 80% of patients, renal transport alone in 20% (242). Amino acid malabsorption of intestinal absorption of neutral amino acids, but no renal aminoaciduria has been observed. A somnolent state has been reported. The MRI is nonspecific; it demonstrates delayed myelination (244).

Diagnosis

Hartnup disease should be considered in patients with intermittent cerebral symptoms, even without a rash.

Numerous metabolic disorders with a partial enzymatic defect produce intermittent cerebellar ataxia and mental retardation, and some of the diseases caused by defects in the urea cycle. Additionally, in familial inborn errors of metabolism (245). Another rare condition to be considered in the differential diagnosis of Hartnup disease is hydroxylation (246). Chromatography of urine for amino acids and indolic substances in the presence of a rash.

Treatment

The similarity of Hartnup disease to pellagra has prompted treatment with nicotinic acid (25 mg/day). The tendency for symptoms to remit spontaneously and for general improvement to occur with improvement in nutrition should be taken into account. Patients should be re-evaluated.

Low Syndrome (Oculocerebrorenal Syndrome)

Low syndrome is a gender-linked recessive disorder whose gene has been localized to the long arm of chromosome 10. It is characterized by mental retardation, myopathy, and congenital glaucoma or cataract. Biochemically, it is marked by lactic acidosis, and hypophosphatemic rickets (248). The gene responsible for the disorder has been cloned and identified as inositol polyphosphate-5-phosphatase, an enzyme that is involved in the conversion of extracellular inositol to inositol trisphosphate. The genetic lesion relates to the basic phenotypic defect, which is believed to be a defect in membrane transport.

Neuropathologic examination has disclosed rarefaction of the molecular layer of the cerebral cortex and dilatation (252,253). The urinary levels of lysine are more elevated than those of the other amino acids. Amino aciduria of the mucosa has been demonstrated in two patients (251).

The clinical picture is that of a developmental delay or of progressive loss of acquired skills. This is associated with a peripheral neuropathy with loss of myelinated fibers (254,255). CT scans reveal reduced density of periventricular white matter, especially in the occipital region (256). T2-weighted MRI shows patchy, irregular areas of increased signal intensity. Cystic lesions have been observed (257).

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