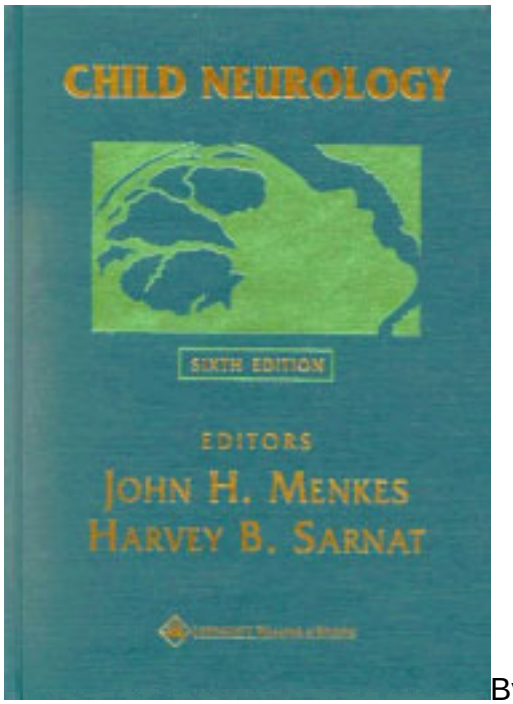
Child Neurology 6th edition (April 15, 2000): by John H. Menkes (Editor), Harvey B. Sarnat, Sam



By OkDoKeY

Child Neurology

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To Joan, my wife, for giving me the pleasure o
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 Edit

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

My predecessors had an easier task. Frank R. Ford, under whose tutelage I had the good fortune t
standard text of pediatric neurology, *Diseases of the Nervous System in Infancy, Childhood and Ad*
inscribing my text, “Doctor, there are many things in here I don't know much about.” Thomas Farme
excellent textbooks of pediatric neurology, but these texts were also published decades ago, and n
both comprehensive and accurate. The one exception is Jean Aicardi's new text, *Diseases of the N*
the laws of gravity.

To obtain a broader point of view, I have therefore called on Harvey B. Sarnat and his expertise in n
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, p
transplantation to help me with the chapter that deals with the neurologic manifestations of systemi
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 b
developments: a lag period of at least 1 year between completion of scientific work and its citation i
retained and sometimes even enlarged the number of classic citations. Too often, younger practitio
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, Ceda
Library for their assistance in preparing the new edition.

Preface to the First Editi

Even in a textbook, prefaces are written not to be read but rather to blunt inevitable criticisms. One
first-rate pediatric neurology texts, was this book ever written. The main excuse for becoming involv
already overwhelmed medical audience, is the hope of being able to offer a new viewpoint of the fie
neurology has felt the impact of the many recent advances in the neurosciences. Their magnitude l
is read. At that time, clinical descriptions achieved a degree of clarity and conciseness, which has r
equaled. Yet the reader who finds the explanation of Tay-Sachs disease* offered during the last ye
achievement at the great strides made during a relatively brief historical period. However, at the sa
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 scie
neurologic disease. Obviously, this can only be done to a limited extent. For some conditions the ba
available experimental data only provide tangential information. Even when biochemical or physiolo
their full presentation has been avoided, for to do so with any degree of completeness would requir
go far beyond the intent of the text. The author and his colleagues have therefore chosen to review
impact, and to refer the reader to the literature for some of the remaining information. They have als
examination of children. This subject is extremely well presented by R. S. Paine and T. E. Oppe, in
seriously interested in pediatric neurology should read.

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

(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 p

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

*Namely, “an inherited weakness of the central nervous system, especially of the ganglion cells, and a premature dege
**London, Wm. Heinemann, 1966.

[There was] . . . a time when theses in medicine could still be beautifully literary, since ignorance ab
art.
—Kurt Vonnegut, Jr.

Be kind to my mistakes, and live ha
—Anonymous translator of *Robinson Crusoe* into Italian; c

Chapter 1

Metabolic Diseases of the Nerv

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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 emphas 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 relativ importance rests in part on the insight they offer into the relationship between a genetic mutation, t nervous system.

The mechanisms by which inborn errors of metabolism produce brain dysfunction remain largely ur pathogenesis has been proposed. Not all enzyme defects lead to disease; a large number of harml 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 r 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 DISOI

The spectacular advances of molecular biology have facilitated the diagnosis and prevention of ger 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 c

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 neur child medical history and physical examination.

Two questions should be considered: What type of patient is suspect for an inborn error of metabol 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 underlyi

Neurologic disorder, including mental retardation repli- cated in sibling or close relative

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

Metabolic Screening

Routine screening of plasma and urine detects the overwhelming majority of disorders of amino aci organic acids, as well as the common disorders of carbohydrate metabolism. At our institution, met organic acids. The yield on these tests is low, and a high frequency of nonspecific or nondiagnostic elevated concentrations of blood ammonia with the patient in the fasting state or on a high-protein i characterized by hypoglycemia or intermittent acidosis. Elevated lactic and pyruvic acid levels in se mitochondrial disorders. Hence, determination of fasting blood sugar, serum pH, pCO_2, and lactic a the suspicion for a metabolic disorder be high, these determinations should be repeated with the ch Other biochemical determinations required in the evaluation of a patient with a suspected metaboli serum carnitine levels (including total, acyl, and free carnitine), immunoglobulins, T_4, T_3, serum cop 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 mu and GM_1 gangliosidosis. Neuroimaging studies, including magnetic resonance imaging (MRI), have Abnormalities such as agenesis of the corpus callosum and a large operculum seen in a few of the much higher when a child with mental retardation with or without seizures is subjected to MRI. As a Thus, the computed tomographic (CT) scanning or MRI shows a significant abnormality in approxim (8). As a rule, MRI provides more information than CT. As is noted in Chapter 2, in the Diseases w 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, number of centers.

Structural and Biochemical Alterations

In a number of metabolic disorders, notably the lipidoses and white matter degenerations, diagnosi ultrastructural, and biochemical studies on biopsied tissue. In the past, a brain biopsy was required structural and biochemical alterations can be detected outside the central nervous system (CNS) in diseases (discussed in Chapter 1 and Chapter 2) are likely to be diagnosed by examination of vari

Tissue studied	Disease
Peripheral nerve	Metachromatic leukodystrophy Globoid cell leukodystrophy Infantile neuroaxonal dystrophy Fabry disease Refsum disease Tangier disease
Skin, conjunctivae, lymphocytes	Most lipidoses, particularly late infantile and juvenile neuronal ceroid lipofuscinosis Lafora disease Neuroaxonal dystrophy* Mucolipidoses Sanfilippo syndrome Fabry disease
Muscle	Late infantile and juvenile neuronal ceroid lipofuscinosis Familial myoclonus epilepsy Mitochondria disorders
Bone marrow	Niemann-Pick disease Gaucher disease GM_1 gangliosidosis
Brain	All lipidoses, and degenerative diseases of gray matter All white matter degenerations, with the possible exception of Pelizaeus-Merzbacher disease None of the movement disorders, except Huntington 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). [$NADP^+$, nicotinami
nicotinamide-adenine dinucleotide phosphate (reduced form).]

PAH is normally found in liver, kidney, and pancreas, but not in brain or skin fibroblasts. The enzym
with a molecular weight of approximately 100,000. The gene coding for the enzyme has been clone
gene is approximately 90 kilobase (kb) long and codes for a mature RNA of approximately 2,400 ba
analysis of patients with PKU and has confirmed that PKU is the consequence of numerous mutant
have been recorded, with the frequency of the mutations differing considerably between ethnic grou
than homozygotes in the precise meaning of the term (12). Some mutations result in little or no PA
significant enzyme activity (13,13a). As a rule, the biochemical phenotype (i.e., the degree of pheny
predicted from the genetic mutation. In the experience of Ramus and colleagues, however, no good
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
4. It is present in normal amounts in classic PKU, but is absent or defective in one type of the non-P

The infant with classic PKU is born with only slightly elevated phenylalanine blood levels, but becau
food proteins and postnatal catabolism accumulates in serum and CSF and is excreted in large qua
converted to phenylpyruvic acid, phenylacetic acid, and phenylacetylglutamine.

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

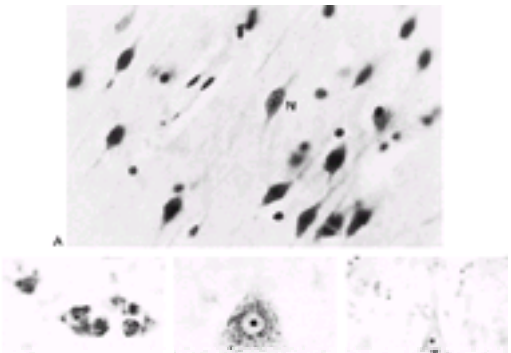
In addition to the disruption of phenylalanine metabolism, tryptophan and tyrosine are handled abno
in PKU, and fecal content of tryptophan and tyrosine is increased. These abnormalities are reverse
Miyamoto and Fitzpatrick suggested that a similar interference might occur in the oxidation of tyrosi
and might be responsible for the deficiency of hair and skin pigment in phenylketonuric individuals
extent 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 ou
Additionally, the amount of Nissl granules is markedly deficient. This is particularly evident in those
arborization and the number of synaptic spikes are reduced within the cortex (17). These changes
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 act
substantia nigra, diminished or absent pigmentation is not a result of tyrosinase inhibition by pheny
phenylketonuric patient must be interrupted at some other metabolic point, such as the metal-cataly
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 pro
By 49 months, delayed intellectual development becomes apparent (20). In the untreated classic c
training. Children in this category have an IQ below 50. Seizures, common in the more severely ret
spontaneously. During infancy, they often take the form of infantile spasms, later changing into toni

The untreated phenylketonuric child is blond and blue-eyed, with normal and often pleasant feature
musty odor, attributable to phenylacetic acid, can suggest the diagnosis. Significant neurologic abn
not unusual. Microcephaly may be present, as well as a mild increase in muscle tone, particularly in
hands is seen in approximately 30% of the subjects. Parkinsonianlike extrapyramidal symptoms als
extensor.

A variety of electroencephalographic (EEG) abnormalities has been found, but hypsarrhythmic patt
multiple foci of spike and polyspike discharges are the most common (22). Neurologic examination
in 40% in the experience of Thompson and colleagues (23). Abnormalities included hyperactive ref

MRI is abnormal in almost every subject, regardless of when treatment was initiated. On T2-weight
subcortical white matter of the posterior hemispheres. Increased signal can extend to involve the de
hemispheres. No signal abnormalities are seen in brainstem, cerebellum, or cortex, although cortica
abnormality is unrelated to the subject's IQ, but is significantly associated with the phenylalanine le
off their diets, resumption of dietary treatment can improve MRI abnormalities within a few weeks o
of the MRI changes are the result of edema (23, 25).

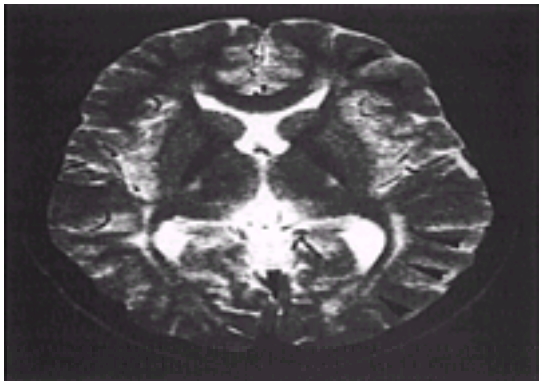


FIG. 1.4. T2-weighted magnetic resonance imaging of a 16-year-old girl with phenylketonuria. The
years of age. At the time of the scan, her neurologic examination was normal, but her phenylalanin
high signal, particularly in the parieto-occipital areas, but also at the tips of the anterior horns of the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

Heterozygous mothers tend to have elevated plasma phenylalanine levels and somewhat reduced

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 reduc levels range between 4 and 20 mg/dL (242 and 1,212 µmol/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).

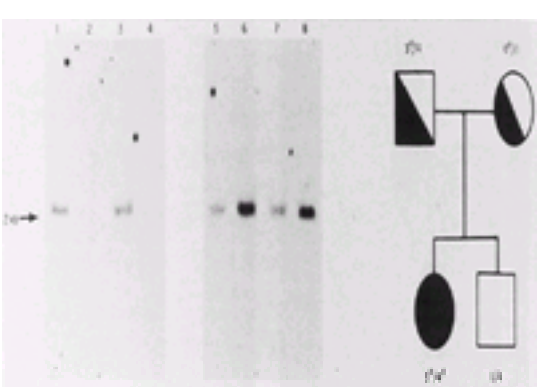


FIG. 1.5. Oligonucleotide hybridization analysis. Lanes 1 and 5, father; lanes 2 and 6, mother; lane unaffected child. A mutant splicing probe specific for the exon/intron 12 splice junction was used fo used for lanes 5 to 8. DNA was isolated from leukocytes of family members, digested with the restr 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 haploty The mother has a mutant haplotype 4 gene and a normal haplotype 1 gene. The mutant splicing pr splicing probe hybridizes strongly (lane 6). The data show that the PKU mutation associated with th associated with the father's mutant haplotype 3 allele. The PKU child in this family inherited the mu gene from his mother. DNA isolated from this child hybridized to both the mutant and the normal sp different mutant phenylalanine hydroxylase alleles, and, consequently, is a compound heterozygote from his father and the normal haplotype 1 allele from his mother. He hybridizes strongly to the nor 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 and many neurologic deficits, are aptly termed *malignant phenylalaninemia*. Biochemically, these c 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 fibroblasts, but normal hepatic PAH activity (46). Dihydropteridine reductase is responsible for the (see Fig. 1.1). BH_4 levels are low in blood, urine, CSF, and a number of tissues. Because BH_4 is ar

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 me avoid symptoms of phenylalanine deficiency, milk is added to the diet in amounts sufficient to maint 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 perfor monthly thereafter.

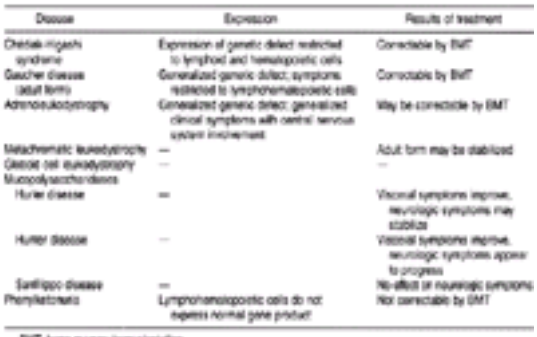
Strict dietary control should be maintained for as long as possible, and most centers strive to keep moderate and mild PKU. Samples of low-phenylalanine menus are given by Buist and colleagues (restricted diet are discussed by Acosta and colleagues (60). Dietary lapses frequently are accompa workers have suggested supplementation of the low-phenylalanine diet with tyrosine, but no statisti outcome. Failure to treat subjects with mild hyperphenylalaninemias does not appear to produce ei

Dietary therapy has for the greater part been effective in preventing mental retardation in patients w on several factors. Most important is the age at which the diet was initiated. Smith and coworkers fo between birth and start of treatment (61). The average phenylalanine concentration while receiving phenylalanine levels in the most recent cohorts being 5.0 to 6.6 mg/dL (300 to 400 µmol/L). Additio length of time that phenylalanine concentration was below 2.0 mg/dL (120 µmol/L)], also affected o the most favorable diagnostic and treatment characteristics have lower IQs than other members of difficulties, and behavioral problems, notably hyperactivity (61,62 and 63). Dietary supplementation improve performance on neuropsychological tests (64). The most likely explanations for these defic by 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 and mai their EEG results tend to revert to normal. Microcephaly, if pres-ent, can correct itself, and abnorma

Considerable uncertainty exists about when, if ever, to terminate the diet (65). In the series of Wais discontinued at 5 years of age had a reduction in IQ of 10 points or more during the ensuing 5 year restrictive diet predicted the change in IQ. Of the children whose IQs dropped 20 or more points, 90 higher, and 40% of those whose IQs rose 10 points or more had a phenylalanine level of less than discontinuation of the diet was accompanied by the evolution of spasticity and worsening of white m diet results in clear clinical improvement and resolution of new MRI abnormalities. Reports such as phenylalanine intake and indicate that dietary therapy for patients with classical PKU should be lifel

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



Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is a familial cerebral degenerative disease caused by a defect i
passage of urine that has a sweet, maple syrup–like odor. It was first described in 1954 by Menkes
diagnosed throughout the world, and its incidence is estimated at 1 in 220,000 births (76). In some
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: a-ketoisocaproic ac
derivatives of leucine, valine, and isoleucine, respectively (78,79). Their accumulation is the conse
ketoacids (Fig. 1.6).

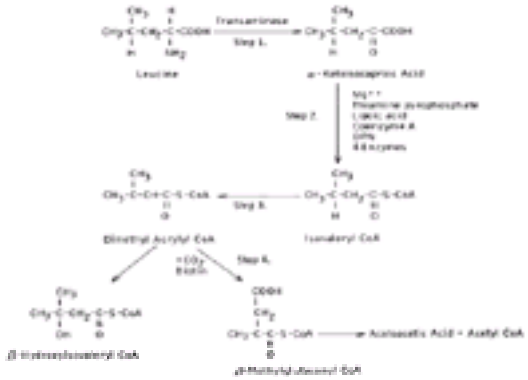


FIG. 1.6. Degradation of leucine in mammalian tissues. In maple syrup urine disease, the metaboli
confined to step 3. A rare entity with a possible metabolic block at step 4 also has been reported.

The branched chain a-ketoacid dehydrogenase complex is located within the mitochondrial inner m
comprising six proteins: E_{1a} and E_{1b}, which form the decarboxylase; E_2; E_3; and a branched chain–s
activity of the complex by phosphorylating and dephosphorylating the dehydrogenase. E_1 is a thian
dihydrolipoyltransacylase, transfers the acyl group from the first enzyme to coenzyme A. The third
reoxidizes the disulfhydryl form of lipoamide. The same enzyme is common to other a-ketoacid deh
dehydrogenase (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, co
for E_{1a}, E_{1b}, E_2, and E_3 have been described, with many MSUD patients being compound heterozyg
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
levels of the respective amino acids (e.g., leucine, isoleucine, and valine) are elevated secondary t
formed by transamination of a-keto-b-methylvaleric acid, also has been found in serum (81). In son
a-hydroxyisovaleric acid (82), are excreted also. Sotolone, a derivative of a–ketabutyric acid, the de
a-keto-b-methylvaleric acid, is responsible for the characteristic odor of the patient's urine and pers

Pathologic Anatomy

Structural alterations in the nervous system in untreated infants with MSUD are similar to, but more

organic acidemias.

Diagnosis

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

Treatment

Treatment consists of restricting the dietary intake of the branched chain amino acids through the u
optimal results, infants should be placed on the diet during the first few days of life and should rece
vigorous treatment of even mild infections is mandatory; a number of children on this synthetic diet

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

Nonketotic Hyperglycinemia

This relatively common family of diseases is marked by genetic and phenotypic heterogeneity, and
symptoms (118). In the infantile form, neurologic symptoms begin during the neonatal period. They
myoclonic seizures, apnea, and progressive obtundation with coma and respiratory arrest. The EE
hypsarrhythmia (119). Nystagmus and a marked depression of the electroretinogram results (ERG)
neonatal period; those who survive are profoundly retarded. A transient neonatal form has been re
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 mon
leading to decerebrate rigidity. Extrapyramidal signs are not uncommon (121). A juvenile form with
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 whit
marked gliosis (122). Partial or complete agenesis of the corpus callosum has been described, an i

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

The basic defect in this condition is localized to the mitochondrial glycine cleavage system, which c
complex reaction requires four protein components and, to date, defects in one or another of three
correlation exists between the clinical expression of the disease and the genetic lesion. The classic
absence of the pyridoxal-containing decarbox-ylase (P protein), and the milder atypical forms with t

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

Argininosuccinic Aciduria

Argininosuccinic aciduria is one of the more common of the urea cycle disorders. The condition is c
accumulation of argi-ninosuccinic acid in body fluids. It was first described in 1958 by Allan and oth

Molecular Genetics and Biochemical Pathology

Argininosuccinic acid is a normal intermediary metabolite in the synthesis of urea (see Fig. 1.7). A
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 lactat
(133). The manner in which children synthesize urea is not clear. It appears likely that in argininosu
substrate accumulates to a concentration at which the decreased substrate-binding capacity of the
levels greater than the Km for the mutated enzyme (134).

Pathologic Anatomy

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

Clinical Manifestations

As ascertained by newborn screening, the incidence of argininosuccinic aciduria in Massachusetts
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 seizure
progression is less rapid, but similar symptoms appear in early infancy. In the majority of patients, i
presenting symptoms are mental retardation, recurrent generalized convulsions, poorly pigmented
Some patients have been seizure free, however, and have presented with little more than learning
have had normal intelligence without treatment (141).

Diagnosis

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

Treatment

Hyperammonemic coma in the neonate caused by any of the urea cycle defects requires prompt in
removal of the excess ammonia, and reduction in the formation of ammonia. Quantitative amino ac
and the infant should be given a high dose of intravenous glucose with insulin to suppress protein c
hemodialysis if available, or by peritoneal dialysis (143). Details of treatment are presented by Brus
Treatment for increased intracranial pressure, which frequently accompanies neonatal hyperammo

The long-term management of an infant who suffers a urea cycle defect is directed toward lowering
possible. This is accomplished by providing the infant with alternative pathways for waste nitrogen
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 red

urine amino acids. The disease was first reported in 1962 by Russell and coworkers (153) and is th 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 male subjects, it can be partial (155). As a consequence, blood ammonia levels are strikingly and c contrasted with normal values of less than 0.1 mg/dL or 50 µmol/L), and CSF ammonia is at least 1 glutamate, and alanine; a striking reduction in plasma citrulline; and an increased excretion of oroti 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 presen hepatic encephalopathy, a striking degree of neuronal necrosis also exists. Electron microscopic ex mitochondria (158).

As a rule, the magnitude of the enzymatic defect correlates with the severity of clinical symptoms. I 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 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 often the consequence of protein ingestion and are accompanied by high blood ammonia levels (1 considerable proportion of the neurologic symptoms, alterations in neurotransmitters, notably quinc 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 ra In symptomatic female subjects, behavioral abnormalities are almost invariable. In the series of Ro and hyperactivity were seen in every patient. Episodic vomiting and lethargy were also invariable. A in 38%, and developmental delay in 35%. Seizures, generalized or focal, were seen in 23% (156). consistently when girls were symptomatic. Other girls are asymptomatic except for an aversion to p Valproate therapy can induce fatal hepatotoxicity in male subjects with OTC deficiency, and in hete

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

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

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

Carbamyl Phosphate Synthetase Deficiency

Carbamyl phosphate synthetase deficiency is a disorder of the urea cycle manifested by a reductio 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 neonata of the enzyme, is usually fatal. In partial CPS deficiency, symptoms appear in infancy and consist c hypotonia or hypertonia, and irregular eye movements. Autopsy reveals ulegyria of cerebral and ce the central part of the brainstem. In contrast to argininosuccinic aciduria, no Alzheimer cells are see 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, altho allelic variants have been described. In some of these, ornithinemia is corrected by treatment with 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 acidem which can induce hyperammonemia (181). In these conditions, the accumulation of organic acids i mitochondrial CPS, and the activities of all five enzymes of the urea cycle are depressed. On a clin cycle defects in that infants with a urea cycle defect are asymptom-atic for the first 24 hours of life, demonstrate tachypnea rather than a respiratory distress syndrome. In contrast to the distressed n acidemias demonstrate ketonuria or ketonemia (182). Asymptomatic hyperammonemia is relatively (183).

Histidinemia

Histidinemia is a harmless metabolic variant that is caused by a defect in histidase, the enzyme tha 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 deficie

Defects in the Metabolism of Sulfur Amino Acids

Homocystinuria

The increased excretion of homocystine is a manifestation of several inborn errors of methionine m thromboembolic episodes, ectopia lentis, and mental retardation. Although discovered as late as 19 (185), the prevalence of homocystinuria varies considerably from one country to another, ranging fr (186). The condition is transmitted by an autosomal recessive gene, localized to the long arm of ch

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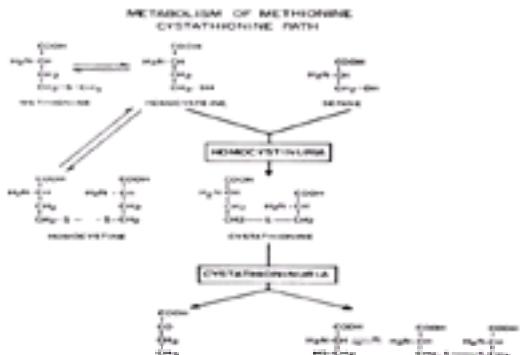
In the most common genetic form of homocystinuria, the metabolic defect affects cystathionine syn from homocysteine and serine (Fig. 1.8) (187). The enzyme as purified from human liver has two id also has been found in brain and skin fibroblasts (189). Considerable genetic heterogeneity exists majority, the lesion resides in a structural gene for the enzyme (190). In most homocystinuric subje of this enzyme, but rather interferes with its activation by pyridoxine (191). As a result, enzyme act proportion of affected families (approximately 25% to 50% of patients with homocystinuria), residua stimulates enzyme activity and partially or completely abolishes the excretion of homocystine, the c patients tend to have a milder phenotype of the disease.



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

Clinical Manifestations

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

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

In approximately 50% of the patients reported, major thromboembolic episodes have occurred on c
pulmonary artery, coronary arteries, and renal artery and vein. Multiple major cerebrovascular accid
closely resembles pseudobulbar palsy. Thromboembolic events are particularly common after ever
cerebral thrombi are the cause of the mental retardation that occurs in 50% of the patients (199,20
proportion of subjects, electromyography suggests myopathy (200).

Radiography reveals a biconcavity of the posterior aspects of the vertebrae (*codfish vertebrae*) (20
childhood. Abnormalities of the hands and feet are noted also. These include metaphyseal spicules
development of the lunate bone (202).

Diagnosis

The diagnosis of homocystinuria suggested by the appearance of the patient can be confirmed by t
methionine and homocystine, and by a positive urinary cyanide-nitroprusside reaction. Enzyme act
specimens.

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

Cystathionine synthase has been found in cultivated amniotic fluid cells, and the condition, therefor

Treatment

Restriction of methionine intake lowers plasma methionine and eliminates the abnormally high urina
methionine free and are supplemented by carbohydrates, fats, and fat-soluble vitamins generally lo
are supplemented with cystine.

Other dietary measures include the addition of folic acid, based on the assumption that the mental
coworkers have recommended treatment with betaine hydrochloride in subjects who do not respon

In pyridoxine-responsive patients, large doses of the vitamin (250 to 1,200 mg/day) reduce or elimi
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 ex

Hyperlysinemia and saccharopinuria were first observed in patients with mental retardation and sei infants and, as is the case for the iminoacidemias, the neurologic abnormalities have turned out to hyperdibasic aminoaciduria. This condition is marked by abnormally high excretion of the dibasic a normal plasma levels and a normal cystine excretion (214).

Increased excretion of lysine and arginine accompanied by hyperammonemia also is seen in famili been recognized, which are probably not allelic. In type I, the presenting symptoms include mental hyperammonemia or protein intolerance (214,215). Type II is not uncommon in Finland, where its i (215). It manifests with protein intolerance, bouts of hyperammonemia, and mental retardation. The of 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 cereb Peroxisomal Disorders, later in this chapter.

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

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

Other Rare Metabolic Defects

A few other extremely rare defects of amino acid metabolism associated with neurologic symptoms the iminoacidemias, cystathioninuria, and histidinemia should caution the reader against accepting number of neurologic disorders that are accompanied by aminoaciduria are not included in Table 1 children are screened, a few exhibit pathologic aminoaciduria. Deficiency diseases, notably rickets, anticonvulsant therapy, can account for some of these; the remainder are unexplained.

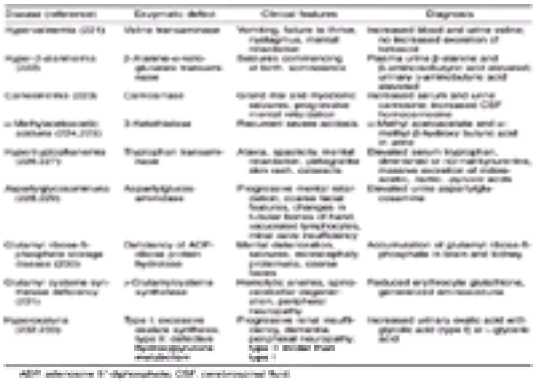


TABLE 1.6. *Some rarely encountered defects of amino acid metabolism associated with neurologic*

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

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

Diagnosis

Hartnup disease should be considered in patients with intermittent cerebral symptoms, even withou

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

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 impr
to evaluate.

Lowe Syndrome (Oculocerebrorenal Syndrome)

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

Neuropathologic examination has disclosed rarefaction of the molecular layer of the cerebral cortex
dilatation (252,253). The urinary levels of lysine are more elevated than those of the other amino ac
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
neuropathy with loss of myelinated fibers (254,255). CT scans reveal reduced density of periventric
especially in the occipital region (256). T2-weighted MRI shows patchy, irregular areas of increase
cystic lesions have been observed (257).