Pathology of Pediatric Gastrointestinal and Liver Disease

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and may abate or disappear without permanent liver injury when homeostasis is restored. Analysis of urine for acylcarnitine compounds and establishment of a fibroblast culture are essential supplements to appropriate tissue samples when clinical suspicion is high. Limited published observations on antemortem liver samples suggest that ultrastructure of mitochondria in FAO are not distinctive in comparison to mitochondrial alterations in primary disorders of electron transport, mitochondrial DNA (mDNA) depletion, and epidemic Reye Syndrome.

13.6.3 Diagnosis

Diagnosis is usually based upon a characteristic abnormal urine acylcarnitine profile determined by high-performance liquid chromatography (HPLC) and plasma acylcarnitine profile determined by fast atom bombardment mass spectrometry from Guthrie card bloodspots, organic acid profiles, and studies of fatty acid processing performed on cultured fibroblasts. Mutation analysis is available for the most common mutations in MCAD.

13.7 Mitochondriopathies

13.7.1 Clinical Manifestations

Mitochondriopathies are abnormalities of energy metabolism caused either by nuclear DNA mutations or mtDNA mutations/deletions that impair oxidative phosphorylation (OXPHOS) (Finsterer 2004; Dimauro 2011). Clinical manifestations in infants or children may involve one or more organs, often in clinically recognizable patterns, but the spectrum differs somewhat from those that affect adults (Bernier et al. 2002). Though enigmas remain, understanding continues to evolve as knowledge and experience expand and the difference between primary and secondary mitochondrial dysfunction due to other metabolic disturbances is clarified.

Mitochondriopathies first recognized, such as those characterized by ragged-red muscle fibers, usually do not affect the liver. Most are caused by maternally inherited mtDNA mutations that typically affect one particular component of OXPHOS system. Clinical manifestations are usually delayed until the proportion of abnormal mitochondria in a given organ, usually skeletal muscle, exceeds a critical threshold that varies with metabolic demand. Large deletions in mtDNA cause Kearns-Sayre syndrome, a myopathy in which the liver is rarely involved, and Pearson marrow-pancreas syndrome. Pearson syndrome, the more common of the two in infants and young children, causes anemia, both exocrine and endocrine pancreas dysfunction, and liver disease that may be clinically significant (Williams et al. 2012). Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem disease that affects young adults but may begin in childhood; the liver is not usually involved (Garone et al. 2011).

Nuclear DNA (nDNA) mutations may affect one p ric acid cycle, stem, or generally impair mtDNA synthesis resulting in multiple defects in OXPHOS. The liver may be affected alone or in various combinations with brain, heart, kidney, skeletal muscle, or gastrointestinal tract.

It is newborn screening.

Acute liver failure due to mitochondriopathy is rare and usually manifest in infants, many of whom have or will develop significant brain disease (Sarzi et al. 2007). One cause, deficiency of cytochrome oxidase (complex IV), associates with many phenotypes, one of which is congenital lactic acidosis, a systemic disease with devastating clinical manifestations that suggest multiorgan dysfunction. Another phenotype, GRACILE syndrome (intrauterine growth restriction, aminoaciduria, cholestasis, hepatic iron overload, and lactic acidosis), is due to mutation in BCS1L, a chaperon protein for complex III, that results in reduced levels of this electron transporter. Still another phenotype, Wolcott-Rallison syndrome, consists of neonatal-infantile diabetes mellitus, skeletal dysplasia, growth retardation, and intermittent liver failure. In these infants, complex I is deficient due to mutation in a nuclear gene, PRK-like ER kinase. Recent

About the ACMG ACT Sheets and Confirmatory Algorithms

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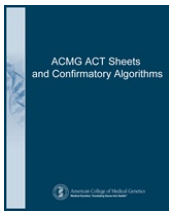
ACMG ACT Sheets and Confirmatory Algorithms [Internet]. Bethesda (MD): American College of Medical Genetics; 2001-.



This resource describes the interrelationships between the conditions screened in newborn screening laboratories and the markers (analytes) used for screening. For each marker(s), there is 1) an ACTion (ACT) sheet that describes the short term actions a health professional should follow in communicating with the family and determining the appropriate steps in the follow-up of the infant that has screened positive, and 2) an algorithm that presents an overview of the basic steps involved in determining the final diagnosis in the infant. By clicking on either the ACT sheet or Algorithm for a particular condition in the column labeled "Links," you will be linked to the corresponding materials.

The algorithms were developed by a work group that included experts in the various specialties and conditions involved in newborn screening for endocrine, hematological, genetic and metabolic diseases. The first page of the ACT sheets includes information that was developed by the experts. It includes links to informational resources to allow the health professional to obtain additional information, if needed. The second page of the ACT sheet includes links to web sites that allow one to identify subspecialists for consultation and referral for the condition(s) described in the ACT sheet. It is supplemented with links to your State Newborn Screening Program and is available for the inclusion of additional health professionals who may be consulted in your area.

All materials were approved by the Board of Directors of the American College of Medical Genetics (ACMG) on December 28, 2009. The materials will be maintained by ACMG over time and additional materials added as new conditions are introduced into newborn screening programs.

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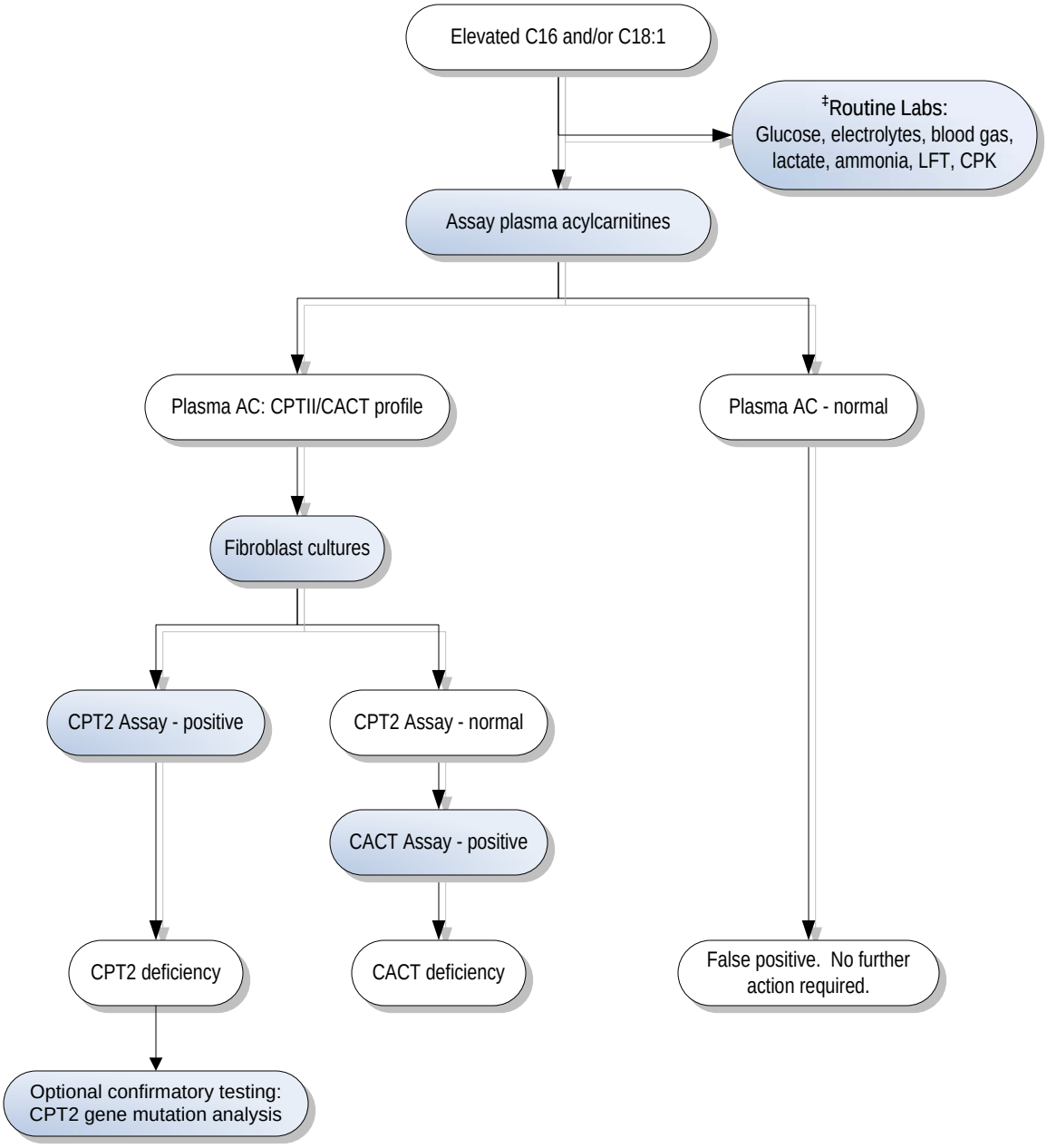
C16 and/or C18:1 Elevated



Abbreviations/Key:
AC = acylcarnitine
CACT = carnitine - acylcarnitine translocase
CPK = creatine phosphokinase
CPT2 = carnitine palmitoyltransferase 2
LFT = liver function tests

‡ = When the positive predictive value of screening is high and the risk to the baby is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

Actions are shown in shaded boxes; results are in the unshaded boxes.

Disclaimer: *This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed* to obtaining the same results. *Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.*

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	< or =7 days (nmol/mL)	8 days-7 years (nmol/mL)	> or =8 years (nmol/mL)
Acetylcarnitine, C2	2.14-15.89	2.00-27.57	2.00-17.83
Acrylylcarnitine, C3:1	<0.04	<0.05	<0.07
Propionylcarnitine, C3	<0.55	<1.78	<0.88
Formiminoglutamate, FIGLU	<0.43	<0.08	<0.14
Iso-/Butyrylcarnitine, C4	<0.46	<1.06	<0.83
Tiglylcarnitine, C5:1	<0.05	<0.09	<0.11
Isovaleryl-/2-Methylbutyrylcarn C5	<0.38	<0.63	<0.51
3-OH-iso-/butyrylcarnitine, C4-OH	<0.13	<0.51	<0.18
Hexenoylcarnitine, C6:1	<0.12	<0.10	<0.15
Hexanoylcarnitine, C6	<0.14	<0.23	<0.17
3-OH-isovalerylcarnitine, C5-OH	<0.08	<0.12	<0.10
Benzoylcarnitine	<0.13	<0.07	<0.10
Heptanoylcarnitine, C7	<0.05	<0.05	<0.06
3-OH-hexanoylcarnitine, C6-OH	<0.08	<0.19	<0.09
Phenylacetylcarnitine	<0.15	<0.22	<0.29
Salicylcarnitine	<0.08	<0.09	<0.09
Octenoylcarnitine, C8:1	<0.48	<0.91	<0.88
Octanoylcarnitine, C8	<0.19	<0.45	<0.78
Malonylcarnitine, C3-DC	<0.09	<0.14	<0.26
Decadienoylcarnitine, C10:2	<0.11	<0.12	<0.26
Decenoylcarnitine, C10:1	<0.25	<0.46	<0.47
Decanoylcarnitine, C10	<0.27	<0.91	<0.88
Methylmalonyl-/succinylcarn, C4-DC	<0.05	<0.05	<0.05
3-OH-decenoylcarnitine, C10:1-OH	<0.12	<0.12	<0.13
Glutarylcarnitine, C5-DC	<0.06	<0.10	<0.11
Dodecenoylcarnitine, C12:1	<0.19	<0.37	<0.35
Dodecanoylcarnitine, C12	<0.18	<0.35	<0.26
3-Methylglutarylcarnitine, C6-DC	<0.28	<0.21	<0.43
3-OH-dodecenoylcarnitine, C12:1-OH	<0.11	<0.10	<0.13
3-OH-dodecanoylcarnitine, C12-OH	<0.06	<0.09	<0.08
Tetradecadienoylcarnitine, C14:2	<0.09	<0.13	<0.18
Tetradecenoylcarnitine, C14:1	<0.16	<0.35	<0.24
Tetradecanoylcarnitine, C14	<0.11	<0.15	<0.12
Octanedioylcarnitine, C8-DC	<0.25	<0.19	<0.19
3-OH-tetradecenoylcarnitine C14:1OH	<0.06	<0.18	<0.13
3-OH-tetradecanoylcarnitine, C14-OH	<0.04	<0.05	<0.08
Hexadecenoylcarnitine, C16:1	<0.15	<0.21	<0.10
Hexadecanoylcarnitine, C16	<0.36	<0.52	<0.23
3-OH-hexadecenoylcarnitine,C16:1-OH	<0.78	<0.36	<0.06
3-OH-hexadecanoylcarnitine, C16-OH	<0.10	<0.07	<0.06
Octadecadienoylcarnitine, C18:2	<0.12	<0.31	<0.24
Octadecenoylcarnitine, C18:1	<0.25	<0.45	<0.39
Octadecanoylcarnitine, C18	<0.10	<0.12	<0.14
Dodecanedioylcarnitine, C12-DC	<0.10	<0.04	<0.04
3-OH-octadecadienoylcarn, C18:2-OH	<0.04	<0.06	<0.06
3-OH-octadecenoylcarnitine C18:1-OH	<0.03	<0.04	<0.06
3-OH-octadecanoylcarnitine, C18-OH	<0.03	<0.05	<0.03

Interpretation

SPECIMEN INFORMATION

Printed By : JDT1303

Specimen # : 20122630554 LastName: JIANHUA
DOC: 09/17/2012 DOR: 09/19/2012 Rptd: 09/21/2012
Name: JIANHUA MR #: 01238373
Mother: CHEN, LIYING Sex: Male
DOB: 09/16/2012 @ 0549 BW: 3316 gms
DOC: 09/17/2012 @ 0810 Twin: Single
AAC: 1 day(s) 2 hour(s) Transfused:
Specimen Age: 2 day(s) Trans Date:
Opt. Use :
Race: Asian/Pacific Islander Ethnic:
HA/TPN: NICU:
Antibiotics: Steroids: 1st screen

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DISORDER	MNEMONIC	STATUS	TEST	VALUE
PTSH	NORM	Normal	PTSH	9.71
MCADD	NORM	Normal	C8	0.07
			C8/C2	0
			C8/C10	0.73
			C10:1	0.07
PKUMS	NORM	Normal	Phe	65
			Phe/Tyr	0.97
GAL	NORM	Normal	GAL	11.57
BIO	NORM	Normal	BIO	
MSUD	NORM	Normal	Leu	82
			Val	86
			Leu/Ala	0.32
			Leu/Phe	1.27
			Val/Phe	1.34
HCYS	NORM	Normal	Met	23
			Met/Phe	0.36
HGB	FA	Normal	HB-IEF	
CF	NORM	Normal	IRT	8.48
CAH	NORM	Normal	CAH	4.14
ASA	NORM	Normal	CITa	10.52
			ASA	1.05
			Cit/Arg	1.86
			Asa/Arg	0.19
CIT	NORM	Normal	CITc	10.52
TYR-I	NORM	Normal	SUAC	0.31
			Tyr	66.35
HMG	NORM	Normal	C5OHh	0.11
			C5OH/C8	1.46
BKT	NORM	Normal	C5:1	0.01
GA-I	NORM	Normal	C5DC	0.05
			C5DC/C5OH	0.44
			C5DC/C8	0.64
			C5DC/C16	0.02
IVA	NORM	Normal	C5	0.07
			C5/C0	0
			C5/C2	0
			C5/C3	0.06
MMAs/PROP	NORM	Normal	C3	1.15
			C3/C2	0.07
			C3/C16	0.46
MCD	NORM	Normal	C5OHm	0.11
CUD	NORM	Normal	C0	30.21
LCHAD/TFP	NORM	Normal	C16OH	0.03
			C16OH/C16	0.01
VLCAD	NORM	Normal	C14	0.28
			C14:1	0.18
			C16	2.52
			C18	0.91
			C18:1	1.07
			C14:1/C16	0.07

Specimen # : 20122720215 LastName: JIANHUA XIE
DOC: 09/25/2012 DOR: 09/28/2012 Rptd: 10/02/2012
Name: JIANHUA XIE MR #:
Mother: CHEN, LIYING Sex: Male
DOB: 09/16/2012 @ 1749 BW: 3317 gms
DOC: 09/25/2012 @ 1200 Twin: Single
AAC: 8 day(s) 18 hour(s) Transfused:
Specimen Age: 3 day(s) Trans Date:
Opt. Use :
Race: Asian/Pacific Islander Ethnic:
HA/TPN: NICU:
Antibiotics: Steroids: 2nd screen.

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DISORDER	MNEMONIC	STATUS	TEST	VALUE
PTSH	NORM	Normal	PTSH	3.7
MCADD	NORM	Normal	C8	0.08
			C8/C2	0
			C8/C10	0.89
			C10:1	0.09
PKUMS	NORM	Normal	Phe	51
			Phe/Tyr	0.51
GAL	NORM	Normal	GAL	9.47
BIO	NORM	Normal	BIO	
MSUD	NORM	Normal	Leu	184
			Val	168
			Leu/Ala	0.36
			Leu/Phe	3.58
			Val/Phe	3.28
HCYS	NORM	Normal	Met	35
			Met/Phe	0.68
HGB	FA	Normal	HB-IEF	
CF	NORM	Normal	IRT	7.05
CAH	NORM	Normal	CAH	5.43
ASA	NORM	Normal	CITa	16.32
			ASA	2.5
			Cit/Arg	1.09
			Asa/Arg	0.17
CIT	NORM	Normal	CITc	16.32
TYR-I	NORM	Normal	SUAC	0.34
			Tyr	99.52
HMG	NORM	Normal	C5OHh	0.13
			C5OH/C8	1.57
BKT	NORM	Normal	C5:1	0.02
GA-I	NORM	Normal	C5DC	0.03
			C5DC/C5OH	0.2
			C5DC/C8	0.32
			C5DC/C16	0.01
IVA	NORM	Normal	C5	0.16
			C5/C0	0
			C5/C2	0.01
			C5/C3	0.19
MMAs/PROP	NORM	Normal	C3	0.87
			C3/C2	0.05
			C3/C16	0.37
MCD	NORM	Normal	C5OHm	0.13
CUD	NORM	Normal	C0	48.83
LCHAD/TFP	NORM	Normal	C16OH	0.02
			C16OH/C16	0.01
VLCAD	NORM	Normal	C14	0.3
			C14:1	0.14
			C16	2.39
			C18	0.92
			C18:1	1.55
			C14:1/C16	0.06

Atlas of Metabolic Diseases

Second edition

William L. Nyhan Bruce A. Barshop and Pinar Ozand

Table 36.1 *Acyl carnitine profiles of plasma in the diagnosis of disorders of fatty acid oxidation*

Disorder	Acylcarnitine	Control reference # μmol/L	Patient range μmol/L	Organic acid analysis
MCAD	C6	0.12	0.12–2.14	Hexanoyl-, suberyl-,
	C8	0.22	1.28–12.24	phenylpropionyl-,
	C8/C8:1	2.32	6.49–46.49	glycine.
	C10:1	0.22	0.26–1.84	Dicarboxylic aciduria
LCHAD	C16/C8:1	2.89	10.8–258.96	3-OH-Dicarboxylic,
	C16OH	0.02	0.12–0.60	Dicarboxylic aciduria
	C18:1OH	0.01	0.14–0.86	
VLCAD	C14:1	0.18	0.76–13.28	Dicarboxylic aciduria
	C14:1/C8:1	1.48	8.26–427.05	
	C14:2	0.08	0.30–3.48	
SCAD/EMA	C4/C3	0.98	0.71–9.0	Ethylmalonic, methyl-
	C4	0.32	0.62–1.28	succinic aciduria,
	C5/C3	0.80	0.19–4.52	Butyrylglycine
	C5	0.22	0.16–0.64	
CPT I**	C0/C16 + 18	2–32	63–291	
CPT II	C14:1/C8:1	1.48	2.50–42.79	
	C16/C8:1	2.89	101.24–221.65	
	C16	0.24	2.06–3.94	
	C16:1	0.08	0.50–0.86	
	C18	0.10	0.64–1.411	
	C16 + C18/C2	0.011–0.095	0.08–0.56	
Multiple acylCoA-dehydrogenase	C4/C3	0.98	0.70–8.19	Isobutyryl-, isovaleryl-,
	C5/C3	0.80	1.39–2.01	2-methyl-butyryl-
	C6	0.12	0.04–3.54	glycine, Glutaric acid,
	C5DC	0.06	0.04–0.08	Dicarboxylic aciduria
Carnitine transporter	C0	–	↓	
	Cesters	–	↓	
Carnitine translocase	C16	2.06–3.94	8.85	
	C18	0.64–1.44	↑	
HMG CoA lyase	C5OH	1.06	0.08–1.42	
	Methyl glutaryl	0.02	0.08–0.62	

Adapted from Vreken *et al.* [9] and other sources

* 95th percentile of the reference range except where a range is given. Abbreviations include EMA, ethylmalonic acidemia, CPT, carnitine palmitoyl transferase; DC, dicarboxylic acid.

** Absence of long chain acyl carnitines.

of the DNA by the polymerase chain reaction. Even in this disease, however, at least five infrequent mutations are known [8], and patients are not being tested for any but the most common one. Acylcarnitine profiling should lead to the diagnosis in each of these disorders [9] (Table 36.1), but experience is not yet available to indicate how often this approach might miss the diagnosis in an established patient who has become carnitine depleted.

During the long fast patients must be monitored closely so that symptomatic hypoglycemia is avoided. Testing is best done in units where the staff has experience with the protocol. An intravenous line is placed to ensure access for therapeutic glucose, and bedside monitoring of blood concentrations of glucose is done at regular intervals. In abnormalities of fatty acid oxidation, fasting must be long enough to exhaust stores of glycogen and require the mobilization of fat and its oxidation. This usually requires 17–24 hours.

The specific enzyme assays for specific disorders are technically demanding and not generally available. A good next step following the fast, if a specific disease is not identified, is to pursue a more general study of metabolism in cultured cells [10,11] in which CoA or carnitine esters are separated and identified by high performance liquid chromatography (HPLC) after interaction with ^{14}C or ^{13}C-labeled hexadecanoate.

Experience with the diagnosis and management of disorders of fatty acid oxidation has now been summarized for a series of 107 patients with a spectrum of disorders [12]. The severity of these diseases is indicated by the fact that only 57 of the 107 patients were alive at report. An additional 47 siblings had died in infancy for a total of 97 deaths, 30 percent in

Fourth Edition

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Inborn Errors of Metabolism

Laurie Smith and Cary O. Harding

PEARLS

- Unexpected and unexplained clinical deterioration in a previously healthy infant or child is an important clue to the presence of an inborn error of metabolism (IEM).
- Loss of previously attained developmental milestones during childhood is an important clue to the presence of a neurodegenerative disorder such as lysosomal storage disease.
- Blood glucose less than 40 mg/dL is distinctly unusual after the first 24 hours of life, particularly in infants who have started feeding, and should be thoroughly investigated.
- Laboratory evaluation for inborn errors of metabolism should be undertaken in any child with a suggestive clinical history regardless of the results of newborn screening. A normal newborn screen, although perhaps reassuring, does not rule out the possibility of an IEM.
- With catastrophic illness in a previously well child without signs of any particular IEM, the "shotgun" diagnostic evaluation should minimally include plasma amino acid analysis, urine organic acid analysis by gas chromatography-mass spectrometry, and a so-called *urine metabolic screen*.

Metabolism can be defined as the sum of all biochemical processes that convert food to smaller molecules and energy for the purposes of structure and function. An inborn error of metabolism (IEM) is an inherited deficiency of any critical step in metabolism. Although genetic deficiency of catalytic enzymes in intermediary metabolic pathways is the classic paradigm for IEM, the pathophysiology of metabolic disorders may involve abnormalities of any number of cellular processes, including transmembrane transport, cell signaling, cell differentiation and development, energy production, and others. Many IEMs are individually rare, although a few, including phenylketonuria (PKU) and medium-chain acyl-coenzyme A (acyl-CoA) dehydrogenase deficiency (MCADD), a defect in fatty acid oxidation, exhibit a population incidence approaching 1:10,000 live births.[1,2] Specific IEMs may be more common in certain ethnic groups with a history of relative reproductive isolation. Collectively, the population incidence of all IEMs may approach 1:1500 live births, depending upon how broadly IEM is defined. Many IEMs are associated with catastrophic illness necessitating advanced life support. Although IEMs may present very rarely within the professional lifetime of the average medical practitioner, critically ill children with IEMs will not be uncommon visitors to the pediatric intensive care unit (ICU), especially in a tertiary care center.

The key to successful treatment of IEMs is the initial suspicion and timely diagnosis of the disorder. Certain features of the clinical history, physical signs and symptoms, and results of routine laboratory studies often suggest the possibility of IEM. Second-tier screening metabolic studies provide further evidence for the presence of a disorder. The results of routine neonatal screening studies may suggest a specific disorder prior to development of any diagnostic suspicion on the part of the clinician or even prior to the onset of symptoms in the neonate. In the case of a critically ill child with a suspected metabolic disease or with an abnormal neonatal screening test result for a specific metabolic disorder, immediate consultation with a biochemical geneticist, even if only by telephone, is paramount. The genetic consultant helps direct the diagnostic laboratory evaluation and recommends nonspecific emergency treatment, if any is warranted, prior to the availability of the definitive diagnostic studies. Communication among the intensivist, genetic consultant, and biochemical genetic diagnostic laboratory is critical to achieving the timely and correct diagnosis of IEM. A satisfactory clinical outcome for the affected child is completely dependent upon the collaborative efforts of this tripartite team approach.

Other published textbooks on the diagnosis and treatment of IEM provide an exhaustive list of known disorders.[3,4] Rather than recapitulate an encyclopedia of possible diseases, this chapter presents a diagnostic rationale based upon specific clinical symptom complexes that are likely to occur in the critically ill child. Algorithms for the differential diagnosis of specific clinical scenarios are given in support of this rationale. Symptoms often begin during early infancy in the biochemically most-severe IEMs; naturally, these IEMs with neonatal onset are the focus of our discussion in this chapter. However, "milder" or late-onset variants of virtually every IEM have been described, with onset of symptoms occurring at all ages, even during adulthood. Some IEMs uniformly present after the neonatal period; age of symptom onset (late infancy, childhood, or adulthood) often is an important clue to the specific diagnosis. The clinical presentation, diagnostic workup, and treatment of neonatal onset disorders provide a paradigm for the evaluation and management of possible IEM in a child of any age.

Pathophysiology of Inborn Errors of Metabolism

Under the classic paradigm, an IEM is associated with deficiency of a specific protein, often a catalytic enzyme, involved in a critical metabolic pathway (Figure 76-1). This deficiency leads to a block in the pathway and the accumulation of the

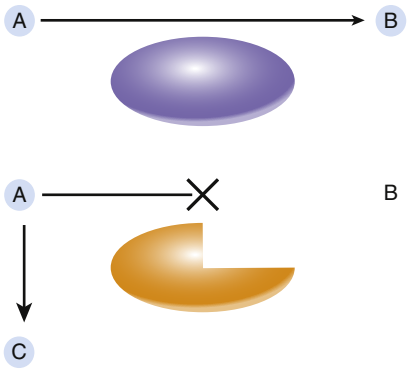

Figure 76–1. Inborn error of metabolism paradigm. Normally, in a given step of intermediate metabolism with intact enzymatic activity, the substrate A is efficiently converted to the product B. In an inborn error of metabolism, deficiency of enzyme activity may lead to excessive accumulation of the substrate; critical deficiency of the product; or production of an alternative, potentially toxic metabolite C through normally quiescent pathways.

enzyme substrate. In this model, three distinct pathogenic mechanisms are possible proximate causes of the symptoms associated with an IEM. The specific pathogenic mechanism involved in any given IEM dictates the appropriate treatment strategy. First, accumulation of the substrate may lead to toxic effects at very high levels; successful therapy requires effective elimination of the substrate or a method to block its toxic effects. An appropriate example for this mechanism is PKU, in which elevated phenylalanine levels adversely affect neuronal development, and the reduction of tissue phenylalanine content through dietary phenylalanine restriction largely prevents the major clinical features of PKU.[5] Second, deficiency of the reaction product, should it be a critically important metabolite, may lead to disease. Supplementation with the essential metabolite, if possible, may cure the disease. Biotin is a required cofactor for four distinct carboxylase enzymes. Deficiency of free biotin develops in the face of genetic biotinidase deficiency and leads to symptoms of multiple carboxylase deficiency. Supplementation with oral biotin completely prevents the clinical manifestations of biotinidase deficiency.[6] The final pathogenic mechanism involves the conversion of the enzyme substrate, through normally quiescent alternative pathways, to toxic secondary metabolites. Elimination or decreased production of these secondary metabolites may improve disease symptoms. For example, tyrosinemia type I (fumarylacetoacetate hydrolase [FAH] deficiency) is associated with recurrent attacks of abdominal pain and paresthesias reminiscent of acute intermittent porphyria. The accumulating substrate, fumarylacetoacetic acid, is converted through secondary pathways to succinylacetone, and succinylacetone in turn inhibits the heme synthetic pathway and causes porphyria-like symptoms. Pharmacologic inhibition of the tyrosine catabolic pathway proximal to the block at FAH decreases the production of fumarylacetoacetic acid and succinylacetone and alleviates the pathology associated with these toxic compounds.[7]

Inheritance of Inborn Errors of Metabolism

IEMs are heritable disorders. The majority of diseases are inherited in an autosomal-recessive pattern, yielding a 25% recurrence risk in future offspring. The gene defects associated with several IEMs are located on the X chromosome. These IEMs, such as ornithine transcarbamoylase deficiency and glycerol kinase deficiency, are inherited in an X-linked pattern. These IEMs are most severe in males, but carrier females may be symptomatic, although usually with less severe or late-onset disease as a result of skewed X-chromosome inactivation. Mutations for several mitochondrial disorders are found on mitochondrial deoxyribonucleic acid (mtDNA). Because mtDNA is exclusively passed from mothers to their offspring, these IEMs exhibit a maternal inheritance pattern but often with variable penetrance and expressivity. Prenatal diagnosis is possible for many IEMs. In addition to allowing for appropriate medical therapy, the timely diagnosis of an IEM in a sick infant or child is important for genetic counseling purposes.

BOX 76–1 Signs And Symptoms of Inborn Errors of Metabolism

Acute illness after period of normal behavior and feeding (hours to weeks)
Recurrent decompensation with fasting, intercurrent illness, or specific food ingestion
Unusual body odor
Persistent or recurrent vomiting
Failure to thrive
Apnea or tachypnea
Jaundice
Hepatomegaly or liver dysfunction
Lethargy or coma
Sepsis
Unexplained hemorrhage or strokes
Developmental delay with unknown etiology
Developmental regression
Seizures, especially if seizures are intractable
Hypotonia
Chronic movement disorder (ataxia, dystonia, choreoathetosis)
Family history of unexplained death or recurrent illness in siblings

Signs and Symptoms of Inborn Errors of Metabolism

Clinical signs and symptoms frequently associated with IEMs are listed in Box 76-1. The symptom repertoire of the critically ill infant is limited, and the clinical presentation of metabolic disorders often is nonspecific. It is for this reason that the diagnosis of an IEM may be easily missed. To maintain maximum diagnostic sensitivity for IEMs, the clinician must maintain a high level of suspicion and be willing to initiate screening metabolic laboratory studies with little provocation. As was true for appendectomies in the era prior to the advent of ultrasound-based diagnosis of appendicitis, a certain number of nondiagnostic metabolic laboratory workups in sick children must be performed to ensure ascertainment of individuals with inherited metabolic disorders. In particular, IEM should be a strong diagnostic consideration in any neonate who has become catastrophically ill following a period of normalcy. This presentation may be clinically indistinguishable from bacterial or viral sepsis, and the nonspecific supportive therapy provided to potentially septic infants (fluid and glucose administration) may alleviate the symptoms and

mask the presence of an IEM. Diagnostic metabolic laboratory studies are most likely to provide definitive information if performed on clinical samples obtained at initial presentation and before any therapy is initiated. Failure to obtain the necessary specimens at this time may miss an important diagnostic window of opportunity. Many children with IEM have been saved initially by intensive but nonspecific treatment but then suffered clinical relapse or even death in the absence of the correct diagnosis. Certainly, the possibility of an IEM should be considered in any child for whom the clinical picture suggests sepsis but the laboratory evaluation for sepsis is negative. Unfortunately, bacterial sepsis is often a complicating factor in critically ill children with IEM. For example, *Escherichia coli* infection (including pyelonephritis, bacteremia, or meningitis) is frequently detected at presentation in infants with galactosemia. The astute clinician remains ever vigilant for the signs and symptoms that may suggest an inherited metabolic disorder.

Recurrent episodes of vomiting and dehydration in response to fasting or intercurrent illness are an important clue to IEM in older infants and children. Feeding difficulties and failure to thrive are common chronic complications. Children with unexplained hypotonia, developmental delay, or movement disorder should be evaluated for possible IEM. Inherited neurodegenerative disorders, such as the lysosomal storage diseases, stereotypically cause developmental regression, specifically loss of previously attained developmental milestones. Several IEMs are associated with major physical anomalies (Table 76-1). When present, these anomalies are exceedingly valuable in suggesting a specific diagnosis and directing the diagnostic evaluation. More commonly, the child with IEM is morphologically normal, and the presenting symptoms are nonspecific. The clinician must then rely upon screening laboratory tests to evaluate the potential for IEM.

Table 76–1 Physical Anomalies Associated with Inborn Errors of Metabolism

Dysmorphic facial features	Peroxisomal disorders Glutaric aciduria type II Smith-Lemli-Opitz syndrome Menkes syndrome Lysosomal storage disorders
Structural brain anomalies	Glutaric aciduria type II (cortical cysts) Pyruvate dehydrogenase deficiency (cortical cysts, agenesis of the corpus callosum) Glycosylation disorders (cerebellar agenesis)
Macrocephaly	Glutaric aciduria type I (with subdural effusions) Canavan disease Alexander disease
Cataracts	Galactosemia Peroxisomal disorders Mitochondrial disorders Lowe syndrome
Lens dislocation	Homocystinuria Sulfite oxidase deficiency Molybdenum cofactor deficiency
Pigmentary retinopathy	Peroxisomal disorders including cherry red spots Lysosomal storage disorders Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Renal cysts	Glutaric aciduria type II, Peroxisomal disorders Mitochondrial disorders
Ambiguous genitalia	Congenital adrenal hyperplasia Smith-Lemli-Opitz syndrome
Skeletal abnormalities	Menkes disease Homocystinuria Peroxisomal disorders Lysosomal storage diseases
Hair or skin abnormalities	Menkes disease Holocarboxylase synthetase deficiency Biotinidase deficiency Argininosuccinic aciduria Phenylketonuria

Laboratory Evaluation of Suspected Inborn Errors of Metabolism

Abnormal results of routine laboratory studies may provide clues to the presence and type of IEM (Table 76-2). Highly informative but sometimes subtle laboratory abnormalities are often overlooked, especially in a busy ICU or hospital ward. For instance, a clinically relevant newborn screening result may have been sent to the primary care provider or birth hospital but not efficiently communicated to the ICU, in a different hospital, to which the now critically ill infant has been admitted. It is imperative to verify the infant's screening results with the primary care provider or newborn screening laboratory (Box 76-2). Calculation of the anion gap, another example of a routine and highly informative result, is key to the differential diagnosis of metabolic acidosis. The absence of urine ketones in hypoglycemic children older than 2 weeks strongly suggests impaired ketogenesis as a consequence of either hyperinsulinism or fatty acid oxidation disorder. On the other hand, fatty acid oxidation and ketogenesis are incompletely developed in neonates. The presence of ketones in the urine of infants younger than 2 weeks is very unusual even during fasting or hypoglycemia and suggests the presence of an unusual keto acid, such as those excreted in maple syrup disease or the organic acidemias. Keto acids, organic acids, and sugars such as galactose or fructose increase urine specific gravity. Urine specific gravity greater than 1.020 in any neonate or in a well-hydrated older child suggests the unexpected presence of an osmotically active substance. Routine urinalysis at many hospitals may not include use of the Clinitest to detect reducing substances. Urine Chemstrips utilize a colorimetric glucose oxidase-based method to specifically detect glucose. This test does not react with any other sugar (galactose or fructose). However, some bedside glucose monitoring systems do react with galactose or fructose; inappropriately elevated capillary blood "glucose" accompanied by a normal venous glucose as measured by chemistry analyzer suggests the presence of a sugar other than glucose in the blood. A comatose infant with a blood urea nitrogen (BUN) level below the limits of detection may have an inherited defect in the urea cycle. Blood ammonia measurement is crucial to confirming that suspicion. Failure to check the blood ammonia level has caused missed diagnoses, failure to appropriately treat hyperammonemia, and further morbidity and mortality in comatose infants with urea cycle disorders

Table 76–2 Initial Laboratory Evaluation of Suspected Inborn Errors of Metabolism

Laboratory Test	Abnormality	Disorder
Complete blood count	Neutropenia Macrocytic anemia Pancytopenia	Organic acidemias Glycogenosis type 1b Cobalamin processing defects Congenital lactic acidoses
Serum electrolytes	Metabolic acidosis	Glycogenoses Organic acidemias FAO disorders MSUD Congenital lactic acidoses
Blood gas	Metabolic acidosis Metabolic alkalosis	Same as above Urea cycle disorders
BUN	Low or undetectable BUN (with hyperammonemia)	Urea cycle disorders
Transaminases (ALT, AST)	Liver dysfunction	Galactosemia Fructosemia Tyrosinemia α1-antitrypsin deficiency FAO disorders Organic acidemias Congenital lactic acidoses Congenital disorders of glycosylation
Total and direct bilirubin	Hyperbilirubinemia	Galactosemia Fructosemia Tyrosinemia α1-antitrypsin deficiency Congenital lactic acidoses
Serum uric acid	Hyperuricemia	Glycogenoses Purine disorders
Blood ammonia	Hyperammonemia	Urea cycle disorders FAO disorders Organic acidemias
Blood lactate	Lactic acidemia	Congenital lactic acidoses Glycogenoses Fructosemia Gluconeogenesis disorders
Urinalysis Odor Color pH Specific gravity Ketones Reducing substances	Unusual odor Inappropriately high specific gravity due to metabolites Ketosis Positive reducing substances	PKU, MSUD, organic acidemias Organic acidemias, galactosemia, fructosemia MSUD, organic acidemias Galactosemia, fructosemia

BUN, Blood urea nitrogen; *FAO,* fatty acid oxidation; *MSUD*, maple syrup urine disease.

or organic acidemias. Finally, bacterial sepsis and meningitis are more common causes of severe lethargy and coma in infants than is IEM, but bacterial infection may also be a complicating feature in severely ill infants with IEM. Infants with galactosemia, for example, are particularly prone to pyelonephritis, bacteremia, sepsis, or meningitis, often with *E. coli*, as noted above. Antibiotic therapy without diagnosis and specific treatment of the underlying disorder may be useful in the short term but does not mitigate long-term IEM-specific effects.

Box 76–2 Screening Metabolic Laboratory Studies for Children with Suspected Inborn Errors of Metabolism

- Plasma amino acid analysis
  Minimum 2 mL blood in a heparin tube
- Urine organic acid analysis
- Urine metabolic screen
  Minimum 10 mL urine

Suspicion of an IEM based upon clinical and routine laboratory findings should initiate specialized biochemical testing (Table 76–3). In the case of severely ill infants or when the clinical suspicion of IEM is very high, consultation with a biochemical geneticist, even if only by phone, is strongly advised to help direct the laboratory investigation and initial therapy. When the clinical presentation is nonspecific, that is, catastrophic illness in a previously well child without signs of any particular IEM, the "shotgun" diagnostic evaluation should minimally include plasma amino acid analysis, urine organic acid analysis by gas chromatography-mass spectrometry, and a so-called *urine metabolic screen*. The battery of qualitative assays included in a urine metabolic screen differs among laboratories, and the ordering clinician should be aware of which tests and disorders are included in the repertoire of the diagnostic laboratory chosen. Furthermore, although diagnostic laboratories in the United States must meet Clinical Laboratory Improvement Amendments requirements and often are accredited by the College of American Pathologists, the testing methodologies used, the quality of diagnostic testing for IEM, and more problematically, the availability of laboratory-associated consultants with experience in the diagnosis and treatment of IEM vary widely among laboratories. Although the ability of clinicians to direct clinical specimens toward specific diagnostic laboratories may be inhibited by contractual arrangements between the hospital and large referral laboratories, the critically ill patient is best served by diagnostic evaluation carried out in a timely manner by an experienced biochemical genetics laboratory, with laboratory staff available by phone for expert consultation on interpretation of test results.

The specific clinical presentation or specific screening laboratory findings may direct the intensivist or biochemical geneticist to order other more specialized metabolic tests (see Table 76-3). These analyses may provide diagnostic confirmation for specific disorders and supportive evidence alone for others. For several IEMs, confirmation of diagnosis may require enzyme activity analysis in tissue (red blood cells, lymphocytes, cultured skin fibroblasts, liver, or skeletal muscle depending upon the specific disorder in question) or molecular DNA testing for a specific gene defect. In general, these tertiary tests, which are often difficult, labor-intensive, and expensive, should be ordered following consultation with a biochemical geneticist. In some instances, confirmatory diagnostic biochemical or molecular tests are available only through specialized research laboratories.

Table 76–3 Biochemical Genetic Laboratory Studies

Specimen	Test	Disorder
Blood	Plasma amino acid analysis	Aminoacidopathies
	Plasma carnitine	Organic acidemias FAO disorders
	Plasma acylcarnitine profile	Organic acidemias FAO disorders
	Serum transferrin electrophoresis	Congenital disorders of glycosylation
Urine	Metabolic screen	
	Ketones	Organic acidemias
	Reducing substances	Galactosemia, fructosemia
	Ferric chloride	PKU
	Dinitrophenylhydrazine	PKU, MSUD
	2,4-nitrosonaphthol	Tyrosinemia
	Cyanide-nitroprusside	Sulfur-containing amino acids
	Mucopolysaccharide screen	Mucopolysaccharidoses
	Qualitative amino acid chromatography	Multiple amino aciduria s
	Organic acid analysis	Organic acidemias FAO disorders
	Acylglycine profile	Organic acidemias FAO disorders
	Quantitative mucopolysaccharide measurement and electrophoresis	Mucopolysaccharidoses
	Qualitative sulfites (Sulfitest) or quantitative sulfocysteine	Sulfite oxidase deficiency Molybdenum cofactor deficiency
	Quantitative succinylacetone	Tyrosinemia type 1
	Quantitative purines	Purine synthesis disorders

PKU, Phenylketonuria; *FAO,* fatty acid oxygenation; *MSUD,* maple syrup urine disease.

Postmortem Evaluation of a Child with Suspected Inborn Errors of Metabolism

Some IEMs, particularly those exacerbated by fasting, may present as sudden infant death. For many IEMs, acute metabolic compensation may be rapid and lethal despite intensive medical intervention. The time after clinical presentation but prior to death may be insufficient to execute an adequate metabolic evaluation. Disease diagnosis is still possible postmortem and is important for fully understanding the cause of death and determining recurrence risk in the family. A protocol for postmortem evaluation of an infant or child with suspected IEM is given in Box 76-3. Many of the biochemical genetic analyses recommended for acutely ill children are still valid on postmortem specimens. Valuable information may be learned from amino acid, carnitine, and acylcarnitine analyses in blood and from metabolic screening and organic acid analysis in urine. However, collection of blood and urine

Box 76–3 Postmortem Biochemical Genetic Evaluation

To be performed on any deceased infant <1 year of age for whom the cause of death is not apparent or any child with suspected IEM.

Analyses are most reliable if obtained within 6 hours after death.

1. Contact newborn screening laboratory for results of neonatal screening.
2. Obtain a 3-mm punch biopsy of skin or Achilles tendon for fibroblast culture.
   - A. Prepare skin with chlorhexidine (Hibiclens) or alcohol. Do not use Betadine because it may inhibit fibroblast growth.
   - B. Use sterile technique.
   - C. Store biopsy specimen in sterile RPMI culture media (if available) at room temperature. May be stored in sterile nonbacteriostatic saline for up to 24 hours prior to culture if culture media is not readily available.
   - D. Send to cytogenetics or biochemical genetics laboratory for culture, possible enzyme analyses, and frozen storage.
3. Collect blood via cardiac puncture (~5 mL per tube).
   - A. One red-top tube at room temperature. Collect and store serum at 70° C.
     - i. Comprehensive metabolic panel (potassium, lipids, uric acid may not be accurate postmortem)
     - ii. If hypoglycemic, insulin, growth hormone, and cortisol levels
   - B. One green-top (sodium heparin) tube at room temperature. Collect and store plasma at 70° C.
     - i. Plasma amino acid analysis
     - ii. Plasma carnitine levels
     - iii. Plasma acylcarnitine profile
   - C. One green-top (sodium heparin) tube at room temperature for cytogenetic (karyotype) analysis.
   - D. If storage disorder suspected, one green-top tube (sodium heparin) at 48° C (wet ice) for leukocyte isolation and diagnostic enzyme analyses.
   - E. One lavender-topp (EDTA) tube at room temperature for CBC.
   - F. One yellow-top (ACD) tube for DNA isolation and possible mutation analysis.
   - G. If infant is <1 year old, spot whole blood onto newborn screening filter paper card for repeat screen.
   - H. Blood lactate and ammonia may not be accurate postmortem.
4. Collect urine (10–20 mL) by suprapubic tap or by swabbing the bladder interior with cotton swab.
   - A. Urinalysis
   - B. Urine reducing substances
   - C. Urine metabolic screen
   - D. Urine organic acid analysis
   - E. If storage disorder suspected, quantitative urine mucopolysaccharide and oligosaccharide analysis
5. If urine is unobtainable, organic acid analysis may be performed on vitreous humor collected by needle aspiration from an eye. Freeze vitreous humor at –70° C.
6. If blood is unobtainable, collect bile (2–3 mL) via puncture of the gallbladder for acylcarnitine profile. Store at –20° C.
7. Collect several biopsies (2 g each) from skeletal muscle, cardiac muscle, kidney, and liver.
   - A. For routine histology, biopsies should be submitted fresh to the pathology laboratory.
   - B. For enzyme analyses, biopsies should be wrapped in aluminum foil, placed in a labeled small specimen container, and immediately frozen in liquid nitrogen. Store at –70° C.

Modified from Steiner RD, Cederbaum SD: Laboratory evaluation of urea cycle disorders. *J Pediatr* 138 (Suppl 1):S21-29, 2001.

may not be possible postmortem, especially if the autopsy is performed many hours after death. In these instances, metabolic testing may be obtained on alternative specimens such as vitreous humor or bile. In the event that screening biochemical studies suggest a specific diagnosis, disease confirmation by enzyme analysis in tissue is highly desirable. Many enzymes can be assayed in cultured fibroblasts; viable fibroblasts may be cultured from skin or Achilles tendon samples obtained as late as 24 hours after death. Biopsies of other organs may be necessary for analysis of certain other enzymes. Muscle, liver, and kidney specimens may be obtained postmortem for enzymatic analysis, but most enzymatic activities in solid organs deteriorate rapidly following death. Collection of specimens as soon as possible after death is critical for valid enzyme analyses.

Emergency Treatment of Children with Suspected Inborn Errors of Metabolism

Laboratory investigation of suspected IEM may require several days to complete, given that the biochemical genetics laboratory may be physically remote from the treating hospital and many of the tests involve complex specimen preparation and analysis. A general approach to the emergency treatment of children with suspected IEM, while awaiting diagnostic studies, is given in Table 76-4. For many IEMs associated with acute catastrophic illness, elimination of the offending metabolite is the key to therapy. Immediate cessation of oral feedings, to stop protein or fat intake, will begin to limit toxin production in disorders of amino acid or fatty acid metabolism. Adequate energy intake as carbohydrate must be supplied, usually parenterally, until a specific diagnosis and definitive treatment plan are available. Dextrose infusion at a high rate suppresses catabolism and reduces the consumption of endogenous protein or fatty acid stores. In extremely recalcitrant cases, insulin infusion drives anabolism and further decreases toxin production. Acute metabolic decompensation in some IEMs (e.g., maple syrup disease) is associated with mild peripheral insulin resistance. Insulin administration (often as little as 0.01 to 0.05 units/kg/hour given by continuous intravenous [IV] infusion or subcutaneous bolus injection) overcomes this resistance and has an immediate impact upon metabolic control. Some clinicians also use anabolic agents such as growth hormone or testosterone to acutely suppress protein and fat catabolism. In certain types of congenital lactic acidosis, particularly defects of pyruvate metabolism, carbohydrate infusion worsens lactic acidosis. Replacement of some carbohydrate with fat as an intralipid infusion may partly reduce blood lactate levels, but infants with this degree of sensitivity to glucose infusion often are difficult to treat and suffer high mortality. Severe hyperammonemia that does not respond to dietary protein restriction and dextrose infusion must be treated by hemodialysis. Ammonia clearance with exchange transfusion or peritoneal dialysis is insufficient to adequately decrease blood ammonia levels. If the results of specialized biochemical genetic diagnostic tests are expected within 2 to 3 days, then parenteral dextrose infusion alone should be adequate to maintain nutrition until a more definitive treatment plan is available. Beyond 3 days, developing essential amino acid and fatty acid deficiencies may induce catabolism of endogenous protein and fat. To prevent this occurrence, enteral or parenteral nutrition with minimal amounts of protein (0.5 g/kg body weight/day) and lipid (20% of total energy intake) should be considered. Empiric administration of cofactors such as the B vitamins is not harmful and may improve metabolite clearance, particularly in disorders caused by deficiency of enzymes that require specific cofactors. Carnitine is required for transport of long-chain fatty acids across the mitochondrial membrane and serves a secondary role in the disposal of excess and potentially toxic acyl-CoA species. Secondary carnitine deficiency is commonly associated with acute metabolic decompensation in organic acidemias and fatty acid oxidation defects. L-Carnitine administration prevents secondary carnitine deficiency and may improve clearance of toxic metabolites; it is lifesaving in specific inherited dilated cardiomyopathies.

Table 76–4 Emergency Treatment of Suspected Inborn Error of Metabolism

Goal	Action
Suppress toxic metabolite production	Discontinue oral feedings
Correct fluid imbalance and electrolyte abnormalities	Appropriate IV fluid management
Correct hypoglycemia	IV dextrose-containing fluid infusion
Correct metabolic acidosis	Intravenous hydration if pH >7.2 Add IV bicarbonate if pH <7.2 Sodium bicarbonate (1 mEq/mL solution), 1 mEq/kg IV push at <1 mEq/min May repeat ×3 until pH >7.2; maximum dose 7 mEq/kg/24 hr
Correct hyperammonemia	Suppress protein catabolism Hemodialysis
Treat infection	Appropriate infectious disease laboratory evaluation and antibiotic therapy
Suppress protein and lipid catabolism	Infuse D_{10}1/2NS at 1.5-2 × maintenance rate Add insulin infusion if hyperglycemic If severe, unrelenting acidosis, consider growth hormone or testosterone therapy to promote anabolism
Empiric cofactor administration	L-carnitine, 25-50 mg/kg/every 6 hours IV if organic acidemia suspected or cardiomyopathy present B vitamin complex, 100 mg each vitamin every day Vitamin B_{12}, 1 mg IM × 1 if macrocytic anemia
Maintain nutritional status (if without enteral feeds ×2 days and without diagnosis of a specific IEM)	Enteral feeds or parenteral hyperalimentation to include: Protein, 0.5 gm/kg/day only Lipid, 20% of total energy intake Carbohydrate to provide at least the minimum necessary energy intake

Classification of Inborn Errors of Metabolism by Clinical Presentation

As mentioned previously, the clinical presentation of IEM in neonates provides a paradigm for the suspicion and evaluation of potential IEM at all ages. The classification outlined

Table 76–5 Features of Group 1 Inborn Errors of Metabolism

Clinical Features	Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Tests
Hepatosplenomegaly Coarse facies Macroglossia Fetal hydrops Macular cherry red spots Bone changes Hypotonia or hypertonia Chronic rhinorrhea Failure to thrive	Liver dysfunction No acidosis Normal ammonia Normal glucose	Neonatal onset: GM1 gangliosidosis Icell disease Sialidosis Galactosialidosis Niemann-Pick type A MPS VII CDG Later onset Tay-Sachs disease Krabbe disease Other MPS syndromes Niemann-Pick B or C	Urine mucopolysaccharides Urine oligosaccharides Serum transferrin electrophoresis Enzyme analysis in serum, lymphocytes or fibroblasts
Hepatomegaly Dysmorphic facies Severe hypotonia Large anterior fontanelle Seizures Epiphyseal calcific stippling on radiograph	Liver dysfunction No acidosis Normal ammonia Normal glucose Adrenal insufficiency	Peroxisomal disorders: Zellweger syndrome Neonatal adrenoleukodystrophy Others	Plasma very long chain fatty acid analysis Functional and genetic analysis of fibroblasts

MPS, Mucopolysaccharidosis; *MPS VII*, Sly syndrome; *CDG*, congenital disorders of glycosylation.

here is adapted and expanded to include late-onset disorders from a neonatal IEM classification system first described by Jean-Marie Saudubray and colleagues.[4,8]

IEMs can be classified into one of three groups by pathogenic mechanism. In group 1 IEMs, the production or catabolism of complex molecules is disturbed. The lysosomal storage and peroxisomal disorders are included in this group. The symptoms of these disorders include permanent and progressive somatic and neurologic abnormalities that develop in utero, are often clinically apparent at birth, and are unaffected by food intake. This group is often distinguished by the presence of somatic abnormalities such as dysmorphic features or hepatosplenomegaly. Typical clinical features, potential neonatal and late-onset diagnoses, and confirmatory diagnostic tests are listed in Table 76-5.

In group 2 IEMs, the symptoms are caused by defects in the production or utilization of energy. This group includes the congenital lactic acidoses, glycogenoses, gluconeogenic defects, and fatty acid oxidation disorders. In group 3 IEMs, clinical symptoms are caused by progressive intoxication in a previously well infant because of accumulation of toxic metabolites proximal to a metabolic block. Often, neonatal onset IEM in groups 2 and 3 can be distinguished by the time of clinical onset relative to birth. The symptoms of a block in energy production or utilization (group 2) may present within hours after birth, whereas symptoms of intoxication (group 3) develop over the first week of life with increasing food intake and accumulation of toxic metabolites. However, variants of many of these disorders may not become clinically apparent for several months or even years after birth.

Group 2 Inborn Errors of Metabolism

Systemic or tissue-specific impaired energy production from food substrates is the unifying feature of disorders classified in group 2. Generalized profound neurologic dysfunction, including severe central hypotonia, coma, and seizures, sometimes with peripheral spasticity or abnormal movements, typifies the clinical presentation. Children with these disorders present with similar clinical phenotypes but are easily separated into four subgroups (A through D) based upon associated results of routine laboratory studies (Table 76-6). Severe refractory generalized motor seizures, often beginning within the first hours after birth, sometimes even prenatally, are the hallmark of subgroup A. Routine laboratory studies (glucose, blood pH, electrolytes, ammonia) are generally normal unless the infant is near extremis, and secondary metabolic abnormalities are present. Several inherited disorders are associated with this phenotype; diagnostic differentiation depends upon clinical evaluation by an experienced pediatric neurologist or geneticist and the judicious use of specialized diagnostic laboratory tests.

The amino acid glycine is an abundant neurotransmitter within the central nervous system (CNS). Inherited deficiency of the glycine cleavage system, which removes glycine from its receptor in the neuronal synapse, causes severe unrelenting generalized seizures and profound developmental arrest. The only ubiquitous laboratory finding is an elevated cerebrospinal fluid (CSF/plasma glycine ratio).[9] Sulfite oxidase deficiency, either as a primary genetic defect or secondary to generalized deficiency of its molybdenum-containing cofactor, is another rare but important cause of neonatal-onset seizures. Recently, infantile-onset pyridoxine-dependent or folinic acid-dependent seizure disorders have both been found to be caused by recessively inherited deficiency of α-aminoadipic semialdehyde (α-AASA) dehydrogenase, an intermediate enzyme in the metabolism of the amino acid lysine.[10] Consequently, all neonates with refractory seizures should be screened for these treatable disorders either through measurement of α-AASA in urine or sequencing of the ALDH7A1 (antiquitin) gene. Profound neurologic dysfunction with seizures is one of many possible clinical presentations of infants with peroxisomal or respiratory chain disorders. Some subtypes of a still expanding list of congenital disorders of glycosylation present with seizures,[11] as do disorders of sterol production such as Smith-Lemli-Opitz syndrome,[12] but these diagnoses are often associated with stereotypic dysmorphic features and anomalies. Finally, disorders of neurotransmitter synthesis should be

Table 76–6 Features of Group 2 Inborn Errors of Metabolism

Clinical Features	Associated Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Testing
SUBGROUP A			
Profound neurologic dysfunction Severe hypotonia Seizures	No acidosis Normal ammonia Normal glucose	Nonketotic hyperglycinemia Sulfite oxidase or molybdenum cofactor deficiency Pyridoxine- or folinic acid-responsive seizures Peroxisomal disorders Respiratory chain disorders CDG Cholesterol synthesis defects Neurotransmitter synthesis defects	Plasma and CSF amino acid analysis Urine sulfocysteine Urine oxypurines Urine α-aminoadipic semialdehyde *ALDH7A1* gene sequencing Plasma very long chain fatty acid analysis Blood and CSF lactate Plasma acylcarnitine Urine organic acids Serum transferrin electrophoresis Plasma sterols CSF neurotransmitters
SUBGROUP B			
Neurologic dysfunction Hypotonia Seizures With severe acidosis ± Liver dysfunction ± Dilated cardiomyopathy	Severe acidosis Lactic acidosis ± Ketosis ± Hypoglycemia ± Anemia	Congenital lactic acidoses Pyruvate dehydrogenase Pyruvate carboxylase Respiratory chain disorders	Blood and CSF lactate Plasma and CSF amino acid analysis Urine organic acids Diagnostic muscle biopsy to include histology, enzyme analysis
SUBGROUP C			
Neurologic dysfunction Vomiting Dehydration Hypotonia Coma ± Hepatomegaly, liver dysfunction ± Dilated cardiomyopathy Triggered by fasting or intercurrent illness	Hypoglycemia No ketones in urine Acidosis ± Hyperammonemia ± Lactic acidosis	Fatty acid oxidation defects: MCAD LCHAD VLCAD CPT II CAT MACD Ketogenesis defects: HMG-CoA lyase MCKAT SCOT	Urine organic acids Plasma carnitine Plasma acylcarnitine profile Diagnostic fasting study Fatty acid oxidation studies in cultured skin fibroblasts Gene-specific mutation analysis
SUBGROUP D			
Neurologic dysfunction triggered by short fast Hepatomegaly	Severe fasting hypoglycemia Lactic acidosis Normal ammonia ± Ketosis ± Hyperuricemia ± Hypophosphatemia	Glycogen storage: Glycogenosis 1 Glycogenosis 3 Fructose 1,6-bisphosphatase deficiency	Diagnostic fasting study Enzyme studies in liver Gene-specific mutation analysis

CDG, Congenital disorders of glycosylation; *MCAD*, medium chain acyl-CoA dehydrogenase; *LCHAD*, long chain 3-hydroxyacyl-CoA dehydrogenase; *VLCAD*, very long chain acyl-CoA dehydrogenase; *CPT II*, carnitine palmitoyltransferase II; *CAT*, carnitine acylcarnitine translocase; *MACD*, multiple acyl-CoA dehydrogenase deficiency (also known as glutaric aciduria type 2); *HMG-CoA lyase*, 3-hydroxy-3-methylglutaryl-CoA lyase; *MCKAT*, medium chain ketoacyl-CoA thiolase; *SCOT*, succinyl-CoA oxaloacetate transferase.

considered in any infant with idiopathic seizures and neurologic dysfunction, especially if a movement disorder, most commonly dystonia, is also present. Abnormal CSF neurotransmitter levels (5-methyltetrahydrofolate, 5-hydroxyindoleacetic acid, homovanillic acid, 3-methyl-DOPA) are the only associated laboratory diagnostic clue in this latter category of disease.

Severe persistent lactic acidosis is the hallmark of the disorders in subgroup B of early-onset energy deficiency diseases. The presence of metabolic acidosis with an elevated anion gap suggests the possibility of lactic acidosis (subgroup B) or an organic acidemia (see group 3, intoxication types); these are differentiated by measurement of blood lactate and urine organic acid analysis. Blood lactate is most reliably measured on arterial blood or a free-flowing sample drawn from an indwelling central venous catheter. Artifactual elevation of lactate in peripheral venous blood samples is nearly ubiquitous and should be confirmed by lactate measurement in a more appropriate sample. Secondary lactic acidosis resulting from asphyxia, poor tissue perfusion, or tissue necrosis is much more common and may be difficult to differentiate from the congenital lactic acidoses. Occult cardiac disease, intracranial hemorrhage, or bowel necrosis must be considered and ruled out in infants with severe lactic acidosis. Congenital lactic acidosis generally persists despite adequate life support measures, including fluid resuscitation and ventilatory assistance. In certain enzyme deficiencies, the blood lactate level may further increase with IV dextrose infusion. Simultaneous measurements of blood and CSF lactate and amino acids are useful for differentiating primary from secondary lactic acidoses. In congenital lactic acidosis, the CSF lactate level often is higher than the blood lactate level, while the CNS is relatively protected from systemic acidosis in secondary lactic acidemias. The

blood pyruvate level is elevated in some congenital lactic acidoses such as pyruvate dehydrogenase deficiency. However, accurate measurement of blood pyruvate is difficult and fraught with false-positive elevations. Elevated plasma alanine (which is measured as part of a plasma amino acid analysis) is a more stable and reliable indicator of pyruvic acidosis, as alanine and pyruvate are in equilibrium. Enzymatic analysis in cultured skin fibroblasts or mitochondria isolated from a fresh muscle biopsy often is necessary to confirm a specific enzyme deficiency.

Children with subgroup C defects present with hypoketotic hypoglycemia, triggered by fasting, metabolic stress, or intercurrent illness. In these disorders, utilization of fatty acids as fuel is impaired. The most common of the fatty acid oxidation defects is MCADD, which occurs in up to 1:10,000 white births. Although fatty acid oxidation and ketogenesis defects may present in the newborn period, particularly in the setting of delayed maternal milk production for exclusively breastfed infants, the first clinically significant episode may not occur for weeks to months or even years after birth. With extended fasting or intercurrent illness where metabolic demand exceeds available energy supply, severe lethargy acutely develops and then progresses to coma. Recurrent vomiting and consequent dehydration may be associated. Sudden infant death after an overnight fast is an all-too-frequent initial presentation in up to one third of infants with fatty acid oxidation defects. Infants who survive may suffer recurrent episodes of fasting or illness-induced coma, leading to progressive CNS damage and permanent disability. Metabolic acidosis (resulting from accumulation of partially oxidized fatty acids or secondary lactic acidosis), hyperammonemia, hepatomegaly and liver dysfunction, and hypertrophic cardiomyopathy may occur during acute metabolic decompensation episodes. Liver histology is typified by severe steatosis. Chronically affected children may exhibit recurrent vomiting, failure to thrive, developmental delay, and muscular hypotonia. Certain disorders that affect oxidation of long-chain fatty acids are frequently associated with recurrent rhabdomyolysis and myoglobinuria (long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency, trifunctional protein deficiency, very-long-chain acyl-CoA dehydrogenase [VLCAD] deficiency, or carnitine-palmitoyl transferase [CPT]-II deficiency) or pigmentary retinopathy and slowly progressive vision loss (LCHAD or trifunctional protein deficiency). Mothers of infants with fatty acid oxidation disorders (particularly LCHAD or trifunctional protein deficiency) may present with acute liver dysfunction during pregnancy with an affected fetus. This may manifest as acute fatty liver of pregnancy or maternal HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. In the affected infant, hypoglycemia (serum glucose <40 mg/dL) with inappropriately low or absent ketone production during a symptomatic episode is the key laboratory finding that leads to suspicion of a disorder in this subgroup. Differentiation of the specific defects requires analysis of urine organic acids and plasma acylcarnitine species. Between episodes, when the child is clinically well, the urine organic acid profile may be completely normal. Acylcarnitine profiles are more consistently abnormal, but both tests, if normal initially, should be repeated on samples obtained during a symptomatic period to absolutely rule out the possibility of a fatty acid oxidation defect. Carnitine is required for normal fatty acid oxidation; long-chain fatty acids are activated to fatty acyl-CoA, then esterified to carnitine by CPT-I on the outer mitochondrial membrane. These acylcarnitine esters are then transported into mitochondria to complete the oxidation process. In fatty acid oxidation defects, the metabolic block leads to accumulation of the fatty acyl-CoA substrate specific to the deficient enzyme; these species appear in blood as acylcarnitine esters. Analysis of plasma acylcarnitine profiles by tandem mass spectrometry often suggests a specific enzyme deficiency in children with suspected fatty acid oxidation disorders.[13] Diagnostic confirmation may require enzyme analysis in liver tissue or radiometric evaluation of fatty acid oxidation in cultured skin fibroblasts. For certain defects, molecular DNA analysis is clinically available. Two disorders, namely, MCADD[14] and LCHAD deficiency,[15] are associated with relatively common disease-causing mutations. Treatment of all disorders in this subgroup is based upon the provision of adequate nonfat calories and prevention of fasting. Generous IV glucose infusion is lifesaving and essential during acute episodes of metabolic decompensation. Chronic dietary therapy is tailored to the specific enzyme deficiency involved. Many practitioners prescribe carnitine supplementation, initially intravenously during an acute episode and later orally, but the efficacy of this intervention has not been formally investigated in any controlled clinical trial, and its use in disorders of long-chain fatty acid oxidation remains controversial.

Hypoglycemia following a short fast of only 4 to 6 hours is highly suggestive of a glycogen storage disease or a disorder of gluconeogenesis such as fructose 1,6-bisphosphatase deficiency. These disorders of energy deficiency are classified in subgroup D. These infants appear healthy while fed but quickly become obtunded and hypotonic with fasting hypoglycemia. Hepatomegaly is a prominent physical feature. During acute hypoglycemia, other biochemical derangements, including lactic acidosis, hypophosphatemia, hyperuricemia, and hypertriglyceridemia, are frequently present. Confirmation of the diagnosis may require a provocative fast under controlled conditions with continuous monitoring and, sometimes, measurement of glycogen content or enzymatic analysis on a liver biopsy specimen. Molecular DNA analyses are increasingly available for a less invasive approach to diagnostic confirmation in this class of diseases.

Group 3 Inborn Errors of Metabolism

Infants with group 3 IEMs display symptoms and a progressive clinical course suggestive of intoxication. In these infants, who appear completely healthy at birth and for the first few days of life, neurologic dysfunction appears as toxic metabolites accumulate with increasing food intake. Initial symptoms may include vomiting and lethargy that progress, perhaps over only a few hours, to complete coma or shock. This specific clinical presentation in particular suggests the possibility of bacterial or viral sepsis; evaluation for infectious disease is entirely appropriate. However, the clinician must remain alert to the possibility of an underlying IEM in a previously healthy infant suffering catastrophic illness within the first days of life. Group 3 IEMs can be subdivided into four subgroups (A through D) based upon specific clinical and laboratory findings (Table 76-7).

Maple syrup urine disease (MSUD), or branched-chain keto acid dehydrogenase (BCKD) deficiency, affects the catabolism of the branched-chain amino acids leucine, isoleucine, and valine and is the only disorder in subgroup A. Affected

Table 76–7 Features of Group 3 Inborn Errors of Metabolism

Clinical Features	Associated Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Studies
Subgroup A			
Neurologic deterioration Coma Abnormal movements Hypertonia Sweet odor	Mild acidosis Normal lactate ± Ketonuria Normal ammonia + urine DNPH test	Maple syrup disease (branched-chain keto acid dehydrogenase deficiency)	Plasma amino acid analysis Urine organic acid analysis
Subgroup B			
Neurologic deterioration Coma Dehydration	Severe acidosis Severe ketonuria ± Hyperammonemia ± Lactic acidosis ± Hypoglycemia ± Neutropenia Negative urine DNPH test	Organic acidemias: Propionic acidemia Methylmalonic acidemia Isovaleric acidemia MCD deficiency Others	Urine organic acid analysis Plasma carnitine levels Plasma acylcarnitine profile Urine acylglycine profile Molecular DNA analysis
Subgroup C			
Neurologic deterioration Coma Seizures Hypotonia ± Liver dysfunction	Severe hyperammonemia No acidosis + Alkalosis Low BUN Normal glucose Normal lactate	Urea cycle disorders (CPS, OTC, ASS, ASL deficiencies) Triple H syndrome (hyperornithinemia-hyperammonemia-homocitrullinuria)	Plasma amino acid analysis Urine organic acid analysis Urine orotic acid Enzyme studies in liver or fibroblasts Molecular DNA analysis
Subgroup D			
Neurologic deterioration Hepatomegaly Liver dysfunction Cholestatic jaundice	Direct hyperbilirubinemia ± Hypoglycemia ± Acidosis ± Lactic acidosis ± Ketosis	Galactosemia Fructosemia Tyrosinemia type 1 Neonatal hemochromatosis Respiratory chain disorders	Urine reducing substances Plasma amino acid analysis Urine organic acid analysis Urine succinylacetone Enzyme studies Molecular DNA analysis

ASL, Argininosuccinate lyase; *ASS*, argininosuccinate synthetase; *BUN*, blood urea nitrogen; *CPS*, carbamyl phosphate synthetase; *DNPH*, dinitrophenylhydrazine; *MCD*, multiple carboxylase deficiency; *OTC*, ornithine transcarbamoylase.

infants present with coma; abnormal body movements including seizures; and, in contrast to many IEMs, hypertonia and opisthotonus. A severe burst-suppression pattern is the typical EEG abnormality. A sweet body odor, concentrated particularly in urine and cerumen, is often present. Mothers with previously affected children can often diagnose MSUD in a new infant by the presence of this odor. Routine laboratory studies may document mild metabolic acidosis and mild ketosis, but normal lactate and ammonia. The branched-chain keto acids that accumulate in MSUD react only slightly with the urine dipstick test for ketones but readily form a flocculent white precipitate with 2,4-dinitrophenylhydrazine (DNPH) in a urine metabolic screen. The presence and specific identities of branched-chain keto acids in urine are confirmed by urine organic acid analysis. Plasma amino acid analysis reveals tremendous elevation of leucine with lesser accumulations of valine and isoleucine. The neurologic symptoms associated with MSUD result entirely from leucine intoxication. Valine and isoleucine, which do not cross the blood-brain barrier as readily as leucine, seem to contribute little to the neurologic phenotype. Reduction of leucine levels in the body is the goal of MSUD treatment.[16] Emergency therapy during the initial clinical episode includes dietary protein restriction and IV infusion of dextrose-containing fluids. Hyponatremia is a common associated feature; IV hydration with hypotonic fluids easily exacerbates this problem. Additionally, leucine accumulates in CSF and brain and is strongly osmotically active. Rapid IV infusion of hypotonic solutions in several instances has led to acute cerebral edema and death. Dextrose solutions containing a minimum of 0.45% saline (one-half normal saline) are essential, but 10% dextrose with normal saline is preferred if the serum sodium concentration is greater than 135 mEq/L. With administration of IV dextrose, mild hyperglycemia secondary to insulin resistance may occur; inclusion of regular insulin (often only 0.05 units/kg body weight/hour) by either IV infusion or subcutaneous injection promotes anabolism, suppresses endogenous protein catabolism, and accelerates leucine clearance. The vitamin thiamine is a cofactor for BCKD; some individuals with BCKD deficiency (usually with a late rather than neonatal presentation) may respond clinically to thiamine supplementation. Oral thiamine (100 mg/day) is often given empirically to determine whether there is any effect on leucine levels. Once the diagnosis of MSUD is confirmed by plasma amino acid analysis, enteral feedings with a medical food that is free of branched-chain amino acids should be initiated, even if the infant is comatose and nasogastric feedings are necessary. Parenteral hydration should continue until results of urine ketone and DNPH tests are negative and full enteral feeds are reestablished. On this regimen, plasma valine and isoleucine levels plummet rapidly, but several days may be required before plasma leucine normalizes. The valine and isoleucine deficiencies that frequently develop on this regimen stimulate endogenous protein catabolism, which impairs reduction of blood leucine, prolongs neurologic impairment, and chronically may be associated with symptoms of protein insufficiency (hair loss, skin breakdown,

growth failure). Therefore valine and isoleucine supplementation (50 to 100 mg/kg/day) is required. Chronic lifelong therapy involves dietary protein restriction and provision of sufficient energy and amino acids in a leucine-free synthetic medical food. Despite this, infants who suffered prolonged severe leucinosis as neonates often exhibit significant developmental disability. Early diagnosis and appropriate therapy critically enhance neurodevelopmental outcome.

Severe ketoacidosis is the hallmark of IEMs in subgroup B, the organic acidemias. Methylmalonic, propionic, and isovaleric acidemias are the most common disorders in this subgroup. Infants with organic acidemia present with catastrophic episodes of vomiting, dehydration, and coma. Hypoglycemia, lactic acidosis, hyperammonemia, neutropenia, or pancytopenia may be associated findings depending upon the specific IEM. The urine dipstick test for ketones is strongly positive, but in contrast to MSUD, little precipitate forms following the addition of DNPH reagent to the urine. Identification of the specific offending organic acid is accomplished by urine organic acid analysis using gas chromatography-mass spectrometry. Diagnostic confirmation may require enzymatic analysis in tissues such as leukocytes, liver, or cultured skin fibroblasts. Molecular DNA analysis is increasingly available as a diagnostic modality as well. Cessation of protein intake, vigorous rehydration with dextrose-containing fluid, and management of acidosis with sodium bicarbonate infusion are the mainstays of emergency management. In severely acidotic patients, especially with associated hyperammonemia, hemodialysis may be useful for quickly removing both ammonia and the offending organic acid with the goal of minimizing CNS damage. IV infusion of L-carnitine (100 to 300 mg/kg/day) assists with the removal of the offending organic acid and prevents secondary carnitine deficiency. Oral L-glycine supplementation has a similar role in certain IEMs, most notably isovaleric acidemia. Chronic therapy is tailored to the specific enzyme deficiency but often involves dietary protein restriction and provision of a synthetic medical food supplying sufficient energy and amino acids. Recurrent episodes of life-threatening ketoacidosis and coma, generally triggered by fasting or intercurrent illness, are often the greatest long-term clinical difficulties.

Advancing dietary protein intake and normal protein catabolism during the first few days of life lead to severe hyperammonemia in infants with urea cycle and allied disorders (subgroup C). The clinical presentation is nonspecific, with progressive vomiting and neurologic dysfunction. Routine laboratory studies are generally deceptively normal, although the BUN often is below the limits of detection in infants who are unable to synthesize urea. No acidosis is present unless the infant is apneic or hypoperfused and secondary lactic acidosis has developed. Most severely hyperammonemic infants demonstrate respiratory alkalosis secondary to Kussmaul-like hyperventilation triggered by cerebral edema. Detection of hyperammonemia is the critical diagnostic key. The blood ammonia level must be measured in any child with acute-onset obtundation without a clear etiology such as trauma. Determination of the specific IEM involved requires analysis of blood amino acids and urine organic acids. Diagnostic confirmation is now often accomplished through molecular DNA analysis of specific genes involved in the urea cycle, but in rare instances, enzyme analysis in liver or for a few defects in cultured skin fibroblasts may yet be necessary if molecular testing is inconclusive. Provision of nonprotein energy and suppression of protein catabolism through IV dextrose infusion are essential, as in the organic acidemias, but emergency hemodialysis to rapidly decrease blood ammonia is absolutely required if any possibility of favorable neurodevelopmental outcome is to be preserved. Ammonia clearance by exchange transfusion or peritoneal dialysis is insufficient to accomplish this goal. Even with prompt hemodialysis, the metabolic derangement in some infants is so severe that little sustained decrease in blood ammonia is observed. Despite aggressive therapy, neonatal-onset urea cycle disorders are frequently lethal. The few infants exposed to hyperammonemia for a prolonged period who, because of extraordinary life-support efforts, survive are often profoundly neurologically impaired. On the other hand, clinical outcome is favorable in cases where blood ammonia levels rapidly correct on hemodialysis. This dichotomy in outcome presents a considerable dilemma to the intensivist faced with these critical treatment decisions. In practice, hemodialysis should be attempted as soon as possible after the discovery of hyperammonemia unless clinical signs of severe permanent CNS damage are already present. Disorder-specific therapy should continue for infants whose blood ammonia levels immediately normalize with hemodialysis. Aggressive life support measures should be limited for those infants with recalcitrant hyperammonemia. Following dialysis, generous IV hydration and provision of nonprotein calories should continue. The amino acid arginine, normally synthesized through the urea cycle, becomes an essential amino acid that must be provided exogenously in urea cycle disorders. L-Arginine hydrochloride is available for IV administration as 10% solution and should be added to the IV fluid bag to give 0.66 g arginine HCl/m^2/day (6 mL/kg/day in infants). The ammonia scavenging agents sodium phenylacetate and sodium benzoate are available as a combined IV solution (Ammonul, Ucyclyd Pharma). Administration of this solution dramatically improves ammonia clearance and is indicated for the acute management of the proximal urea cycle disorders, but it is associated with severe adverse effects including metabolic acidosis and erosive gastritis if administered inappropriately. Ammonul should be used only in consultation with a provider experienced with its administration and with careful monitoring. Long-term therapy is based upon dietary protein restriction and oral L-arginine or L-citrulline supplementation. Oral administration of sodium benzoate or sodium phenylbutyrate (Buphenyl, Ucyclyd) as ammonia scavengers is often prescribed. Episodes of fasting- or illness-induced hyperammonemic coma frequently recur. Management of recurrent hyperammonemia in a patient known to have a urea cycle disorder is similar to that outlined earlier but can be tailored to the specific defect. Liver transplantation is a viable treatment option for individuals suffering recurrent hyperammonemia and chronic clinical and developmental difficulties despite adequate nutritional and medical therapy.

Hepatomegaly, liver dysfunction, and cholestatic jaundice in association with neurologic deterioration are the central presenting features of IEM in subgroup D. For all of these disorders, the accumulating toxin is particularly damaging to hepatocellular function. Hypoglycemia, acidosis, and mild ketosis may be present. Bacterial infection, particularly urinary tract infection, bacteremia, or meningitis, often caused by *E. coli* or other gram-negative enteral flora, is a frequent occurrence in infants with galactosemia. The specific diagnosis is suggested by the clinical scenario and by the results of

screening laboratory studies. Infants with this clinical presentation who are breastfed or receiving cow's milk-based infant formula are at risk for symptoms of galactosemia, given that lactose (milk sugar) is a disaccharide of galactose and glucose. Infants receiving exclusively soy milk-based formula ingest little galactose. The predominant dietary carbohydrates in soy formula are fructose and glucose, so infants fed soy formula who have this clinical presentation are likely to have fructosemia rather than galactosemia. More typically, infants with fructosemia present clinically after the introduction of fruit to their diet. In either galactosemia or fructosemia, reducing sugars are detected in urine following ingestion of the offending sugar by the urine reducing substance test (Clinitest). Plasma tyrosine level is elevated, urine organic acid analysis displays metabolites from the tyrosine pathway, and succinylacetone is detected in the urine of children with tyrosinemia type I (fumarylacetoacetate hydrolase deficiency). Neonatal hemochromatosis can be diagnosed only on liver biopsy by staining for iron. Diagnostic confirmation differs for each disorder but may include further metabolite analyses, enzymatic analysis in tissue, or molecular DNA testing. Initial therapy is nonspecific: cessation of enteral feeding and IV infusion of dextrose-containing fluid. Once the exact diagnosis is known, a specific therapy plan can be developed. For the carbohydrate disorders, the offending sugar must be reduced or eliminated from the diet. Galactosemic infants are fed soy-milk based formulas only. After weaning, ingestion of dairy products, including baked goods prepared with dairy products, is strictly avoided. Similarly, fructosemic individuals must strenuously avoid any fructose-containing foods. In prior eras, cirrhosis and liver failure were the inevitable outcomes in children with tyrosinemia type I unless they received a liver transplant. Effective therapy that prevents liver degeneration in tyrosinemia has now been developed. The oral drug 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC) blocks tyrosine metabolism upstream from FAH and prevents accumulation of the intermediate metabolites that are toxic to hepatocytes.[17] This medication was highly successful in preventing cirrhosis in two separate clinical trials and has been approved by the United States Food and Drug Administration for general use. The long-term efficacy of NTBC therapy, particularly with regard to the incidence of hepatic adenoma, a common complication of tyrosinemia I, has yet to be proven.[18]

Summary

Most IEMs with symptom onset in the neonatal period emerge as one of the clinical presentations described. As mentioned previously, many of these IEMs have milder or late-onset forms that present with identical symptoms as described, but months or years after birth and often following the stress of fasting or intercurrent illness. These clinical scenarios provide a framework for the recognition, initial evaluation, and emergency treatment of infants with IEM. The remainder of this chapter focuses upon the differential diagnosis of select clinical situations encountered in the pediatric intensive care unit.

Metabolic Acidosis

The key to the differential diagnosis of metabolic acidosis is calculating the serum anion gap ($Na^+ - [Cl^- + HCO_3^-]$). This calculation, normally 10 to 15 mmol/L, represents the unmeasured negative ions, predominantly albumin, in blood. Normal anion gap acidosis (low serum HCO_3 but normal anion gap) is caused by excess bicarbonate loss from either the gut (diarrhea) or kidney (renal tubular acidosis). An elevated or so-called *positive anion gap* suggests the presence of another unmeasured anion. Incidentally, a low serum anion gap may be seen in extreme hypoalbuminemia, as occurs in nephrotic syndrome (see Chapters 68 and 71).

The differential diagnosis of positive anion gap metabolic acidosis in children is similar to that of adults (e.g., using a favorite mnemonic, such as MUDPILES or KETONES), but with the addition of another class of acidoses, the IEMs. Poisoning with methanol, ethanol, paraldehyde, isoniazid, or salicylates can be readily ruled out by history or drug screen. Uremia is also easily discovered by laboratory evaluation. The most common etiologies of a positive anion gap acidosis in children are ketosis, lactic acidosis, or a combination of the two. Extreme dehydration can cause both ketosis and lactic acidosis; these abnormalities are readily corrected with vigorous parenteral rehydration with dextrose-containing fluids. Persistent lactic acidosis suggests ongoing tissue damage from hypoxemia, hypoperfusion, or, more rarely, an inborn error of mitochondrial metabolism. It should be remembered that several organic acids, such as propionic and methylmalonic acids, react with the urinary ketones dipstick. These pathologic organic acids can be differentiated only from the more typical ketones, 3-hydroxybutyric and acetoacetic acids, by urine organic acid analysis. Severe positive anion gap metabolic acidosis that cannot be easily explained by the clinical context, especially if it occurs recurrently or is recalcitrant to parenteral fluid therapy, suggests an inborn error of organic acid metabolism and should be evaluated with a battery of screening metabolic studies, including plasma amino acid analysis, urine organic acid analysis, and urine qualitative metabolic screen.

Hypoglycemia

Hypoglycemia can be defined as a blood glucose concentration less than 40 mg/dL.[19] Low blood glucose may be present within the first few hours after birth, especially in preterm or low-birth-weight infants, but the capacity for effective gluconeogenesis and fatty acid oxidation is induced within the first day after birth. Therefore blood glucose less than 40 mg/dL is distinctly unusual after the first 24 hours of life, particularly in infants who have started feeding, and should be thoroughly investigated (Fig. 76-2). A review of hypoglycemia in infants and children along with a useful diagnostic algorithm have been published.[20] A detailed medical history and careful physical examination are essential to discovering the cause of hypoglycemia. The timing of hypoglycemia relative to feeding is a critical item of historical information. Persistent or postprandial hypoglycemia suggests hyperinsulinism. Hypoglycemia after a short fast (3 to 6 hours) along with permanent hepatomegaly suggests a glycogen storage disorder. Hypoglycemia following a longer fast (8 to 12 hours) suggests a defect in gluconeogenesis or a problem with utilization of fatty acids. The presence of ketones in urine (as measured qualitatively by urine dipstick) or in serum (quantitative measurement of 3-hydroxybutyrate or acetoacetate) is an important clue to the etiology of hypoglycemia. Ketosis during hypoglycemia demonstrates that insulin secretion is appropriately suppressed and that fatty acid mobilization and oxidation are

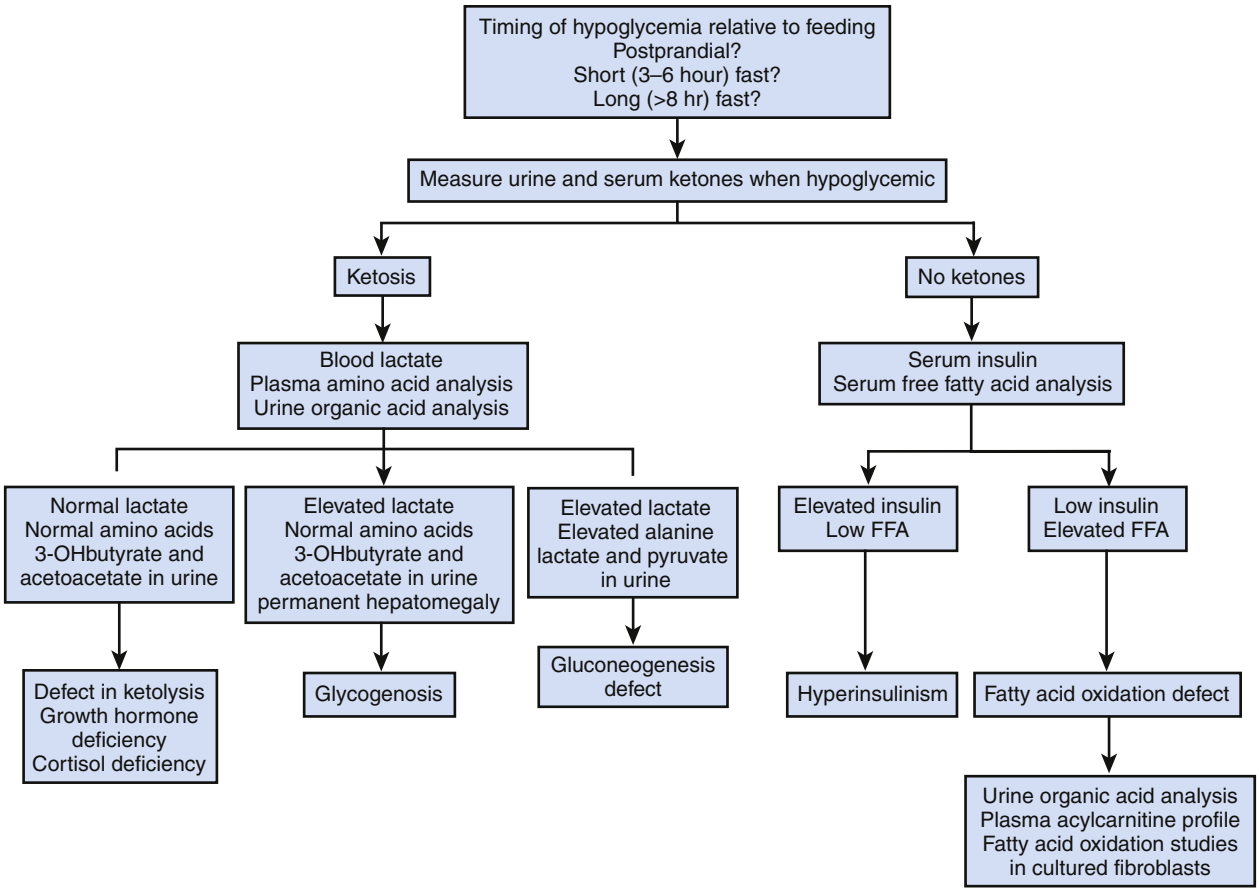

Figure 76–2. Algorithm for evaluation of hypoglycemia in children. *FFA,* Free fatty acid.

intact. Glycogen storage disorders, gluconeogenic defects, and defects of ketone utilization all are associated with ketosis. The absence of ketogenesis during hypoglycemia suggests that either insulin levels are inappropriately elevated or fatty acid oxidation is blocked. An important caveat to this rule is that infants younger than approximately 1 week cannot normally produce enough ketones during fasting to trigger a positive urine dipstick test for ketones. The absence of urine ketones in an infant younger than 1 week does not contribute to the differential diagnosis of hypoglycemia. On the other hand, serum ketones increase with fasting even in neonates, and this test provides a valuable result in the investigation of hypoglycemia. In hypoketotic hypoglycemia, measurement of total serum free fatty acids provides further useful diagnostic information. During fasting, insulin secretion normally is suppressed, free fatty acids are mobilized into circulation from peripheral adipose tissues, and ketones are produced by oxidation of fatty acids in liver. A low serum total free fatty acid level during hypoketotic hypoglycemia strongly suggests inappropriate insulin secretion, even if insulin levels do not appear to be dramatically elevated. Hypoketotic hypoglycemia in association with elevated serum total free fatty acids suggests a defect in fatty acid oxidation.

The importance of treating hypoglycemia cannot be overemphasized as affected individuals are at high risk for seizures and permanent brain damage.[21] After appropriate diagnostic studies are obtained, hypoglycemia should be treated with IV glucose administration at the rate of normal hepatic glucose production, approximately 10 mg glucose/kg body weight per minute or 150 mL/kg per day of a 10% solution until the underlying disorder is identified and more appropriate therapies can be initiated.

Hypoketotic hypoglycemia with low serum total free fatty acids suggests hyperinsulinism. Hyperinsulinism presenting in the newborn period may be caused by intrauterine exposure to elevated glucose levels (maternal diabetes mellitus), familial hyperinsulinemic hypoglycemia (defect in the sulfonylurea receptor), or hyperammonemia/hyperinsulinism syndrome (abnormality in regulation of insulin secretion secondary to mutation in glutamate dehydrogenase). Infants with hyperinsulinism often are obese and require glucose infusions greater than 10 mg/kg/min to maintain normoglycemia. Glucagon administration (0.03 mg/kg, up to 1 mg total dose) reverses hypoglycemia in hyperinsulinism. Oral diazoxide has not been shown to be efficacious in most neonatal cases; however, it can be effective in normalizing blood glucose levels in patients who have infantile forms of hyperinsulinism, including hyperammonemia/hyperinsulinism syndrome.[22] This usually is given at doses of 5 to 10 mg/kg/day divided into three doses. When initially administered, it is given along with glucose and glucagon. The efficacy of diazoxide is defined by demonstrating normal preprandial and postprandial glucose concentrations after overnight fasting and after having stopped IV glucose and any other medications for 5 consecutive days.

Hypoketotic hypoglycemia with elevated serum total free fatty acids, usually occurring following an extended fast (8 to 12 hours) or in association with an intercurrent illness, suggests a defect in fatty acid oxidation. The clinical presentation

of fatty acid oxidation disorders has been described. Although inherited deficiency of at least nine different enzymatic steps in the mitochondrial β-oxidation pathway has been described, the clinical presentation of infants and children with these diseases is stereotypically similar and can be differentiated only by appropriate metabolic testing. In all cases, vigorous hydration with dextrose-containing parenteral fluids is lifesaving. Fasting avoidance is key to long-term treatment and prevention of hypoglycemic episodes.

Infants and children with glycogen storage disorders present with hypoglycemia and permanent hepatomegaly. Hypoglycemia in these disorders is poorly responsive to glucagon administration. Enzymatic defects affecting glycogen synthesis, including glycogen synthase deficiency (GSD-0), as well as defects in glycogen breakdown, such as debranching enzyme deficiency (GSD-III), result in hypoglycemia. Glycogen synthase deficiency usually presents as severe morning hypoglycemia with hyperketonemia and low lactic acid and alanine. Debranching enzyme deficiency results in hypoglycemia secondary to limitation of glucose release from the outer branches of the glycogen molecule. Ketosis is present in GSD-III as the body attempts to generate fuel by increased fatty acid oxidation. Furthermore, the gluconeogenesis pathway is intact; thus hypoglycemia is much milder. In glucose 6-phosphatase deficiency (GSD-1a) and glucose 6-phosphate translocase deficiency (GSD-1b), hypoglycemia usually is apparent 2.5 to 3 hours postprandially as these disorders not only affect glucose release from glycogen but also disrupt gluconeogenesis. Individuals with these disorders have lactic acidosis, ketosis, and hyperuricemia in addition to hepatomegaly.

Hypoglycemia following a longer fast (8 to 12 hours) suggests a defect in gluconeogenesis, ketogenesis, ketolysis, or fatty acid oxidation. Fructose 1,6-bisphosphatase, a disorder of gluconeogenesis, presents as fasting hypoglycemia but also with metabolic decompensation following fructose ingestion. Ketonemia and lactic acidemia are major features, in addition to the hypoglycemia. The ketone synthesis defects that present with fasting hypoketotic hypoglycemia include 3-hydroxy-3-methylglutaryl-CoA synthase deficiency and 3-hydroxy-3-methylglutaryl CoA lyase deficiency. These patients have hypoglycemia in combination with normal blood lactate but no ketonuria. Infants with 3-hydroxy-3-methylglutaryl CoA lyase deficiency also are hyperammonemic. Defects in succinyl-CoA oxoacid transferase and methylacetoacetyl-CoA thiolase represent ketolysis defects. Although the consistent biochemical abnormality is severe ketoacidosis, hypoglycemia also can be seen. Blood lactic acid and ammonia concentrations usually are normal.

Cardiomyopathy and Inborn Errors of Metabolism

Cardiomyopathies, as a rule, are rare. Studies undertaken by the Pediatric Cardiomyopathy Registry have determined that the overall annual incidence is 11.8 per 1 million patient-years and that the incidence was higher in children younger than 1 year than in those between 1 and 18 years old.[23] In this regional study, 40% of cases were hypertrophic cardiomyopathies, 49% of cases were dilated cardiomyopathies, 3% of cases were restrictive or other types, and 8% were unspecified. Further study revealed that of cases of hypertrophic cardiomyopathy, 16% had an identifiable IEM as the underlying cause. These causes included disorders of glycogen metabolism (5%), mucopolysaccharide metabolism (4%), oxidative phosphorylation (5%), and fatty acid metabolism (2%). In the cases of dilated cardiomyopathy, 5% were found to be of a metabolic etiology with disorders of glycogen metabolism (1%), mucopolysaccharide metabolism (2%), and oxidative phosphorylation (2%) as the recognizable underlying cause. Thus it is important to consider IEM in the differential diagnosis of any child with dilated or hypertrophic cardiomyopathy. Because the prevalence of underlying metabolic disorders is so high, some authors have recommended that all children with cardiomyopathy undergo metabolic screening, including blood lactate, plasma amino acid analysis, urine organic acid analysis, urine metabolic screening (particularly for the detection of excessive urinary mucopolysaccharides), plasma carnitine levels, and plasma acylcarnitine profile (Box 76-4).[24] Additionally, serum creatine kinase (CK) should be measured to exclude muscular dystrophy.

Box 76–4 Screening Laboratory Studies for Evaluation of Cardiomyopathy

Blood lactate
Serum creatine kinase
Plasma amino acid analysis
Urine organic acid analysis
Urine metabolic screening
Plasma carnitine levels
Plasma acylcarnitine profile

Autosomal dominant hypertrophic cardiomyopathy has an incidence of 1:500 but demonstrates extremely variable penetrance. Mutations in genes encoding structural sarcomeric proteins are frequent causes of dominant hypertrophic cardiomyopathy. More than 140 mutations in 15 different genes have been identified.[25]

Cardiomyopathy may be a complicating feature of several IEMs (Table 76-8), but with a few exceptions, other associated symptoms or physical examination findings at the time of presentation point toward the appropriate diagnosis. Very broadly, the pathogenesis of cardiomyopathy in IEMs is either myocardial energy deficiency, as occurs in the dilated cardiomyopathy associated with several organic acidemias, or excessive storage of complex molecules in the heart, as occurs in the hypertrophic cardiomyopathy of mucopolysaccharidoses such as Hurler syndrome. Cardiomyopathy occurs as the sole initial clinical manifestation in a relatively restricted list of metabolic diseases, including autosomal recessively inherited deficiency of the cellular carnitine transporter, fatty acid oxidation disorders, glycogenosis types II and IX, and disorders of oxidative phosphorylation. The carnitine transporter defect is caused by deficiency of the sodium-dependent transporter OCTN2, which is responsible for transporting carnitine from the circulation into tissues including cardiac and skeletal muscle.[26] Dilated cardiomyopathy with symptoms of heart failure generally presents within the first years of life and is associated with severely low plasma total carnitine levels. Cardiac function improves dramatically after carnitine supplementation, and cardiomyopathy rarely recurs if carnitine is continued.

Hypertrophic cardiomyopathy resulting from myocardial steatosis may be an isolated presenting feature in several disorders of fatty acid oxidation, particularly those affecting

Table 76–8 Cardiomyopathy and Inborn Errors of Metabolism

Cardiomyopathy as the sole or key presenting feature	Carnitine transport defect
	Fatty acid oxidation defects including: VLCAD deficiency Mitochondrial trifunctional protein deficiency Carnitine palmitoyltransferase deficiency
	Glycogen storage disease type II (Pompe disease)
	Glycogen storage disease type IX (phosphorylase b kinase deficiency)
	Disorders of oxidative phosphorylation (mitochondrial myopathy)
Cardiomyopathy as a secondary feature	Organic acidemias, including: Propionic acidemia Methylmalonic acidemia 3-methylglutaconic aciduria D-2-hydroxyglutaric aciduria Biotinidase deficiency
	Glycogen storage disease type III
	Glycogen storage disease type IV
	Mucopolysaccharidoses
	Congenital disorders of glycosylation
	Congenital myotonic dystrophy
	Congenital muscular dystrophies

VLCAD, Very long chain acyl-CoA dehydrogenase.

long-chain fatty acid metabolism such as VLCAD or mitochondrial trifunctional protein deficiencies. Saudubray et al.[27] examined a series of 109 patients with fatty acid oxidation defects and found that cardiac involvement, including hypertrophic cardiomyopathy or arrhythmia, was apparent at presentation in 51% of cases. Fatty acid oxidation disorders are most reliably detected by analysis of plasma acylcarnitine profiles by tandem mass spectrometry. Long-chain fatty acids are activated to CoA derivatives and then esterified to carnitine prior to transport into mitochondria for β-oxidation. In fatty acid oxidation disorders, especially during acute metabolic decompensation, acylcarnitine species accumulate in plasma and provide a diagnostic profile that is specific to a given enzyme deficiency. Confirmation of the diagnosis may require enzymatic analysis in cultured fibroblasts or mutation analysis. Once the diagnosis of a long-chain fatty acid oxidation disorder has been established, restriction of dietary long-chain fat intake and provision of medium-chain triglyceride oil as an alternative fuel source for the myocardium often reverses cardiomyopathy. Cardiac support measures, including extracorporeal membrane oxygenation, may be necessary for as long as 1 to 2 weeks after presentation before heart function improves.

Glycogen storage disease type II (acid α-glucosidase deficiency; Pompe disease) is a disorder of lysosomal glycogen accumulation that frequently presents as hypertrophic cardiomyopathy, yielding the classic "boot-shaped" radiographic appearance of the cardiac silhouette. Skeletal myopathy manifesting as severe hypotonia may complicate the presentation. Confirmation of the diagnosis requires measurement of enzyme activity in skeletal or cardiac muscle or cultured fibroblasts. In the past, treatment has only been supportive, but enzyme replacement therapy is now available. IV infusion of recombinant acid a-glucosidase every other week has led to improved cardiac function, neuromuscular development, and survival in infants with Pompe disease.[28] However, antibody formation against the drug in some infants, with subsequently decreased treatment effectiveness, remains a clinical problem.

Myocardial function is highly dependent upon mitochondrial oxidative phosphorylation; up to 30% of the total myocardial volume is composed of mitochondria.[29] Dilated or hypertrophic cardiomyopathy is a frequent presenting feature in infants with severe defects of mitochondrial oxidative phosphorylation. Skeletal muscle myopathy, liver dysfunction, renal tubulopathy, bone marrow failure, or CNS abnormalities may occur. Chronic lactic acidosis, if present, is an important indicator of mitochondrial dysfunction. Screening metabolic laboratory studies demonstrate nonspecific abnormalities associated with chronic lactic acidosis. Definitive diagnosis requires histologic evaluation of skeletal muscle and measurement of respiratory chain enzyme activities. Isolated deficiency of cytochrome c oxidase (COX or complex IV) and reduced nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase (complex I) of the mitochondrial respiratory chain are the most common oxidative phosphorylation defects presenting with cardiomyopathy. Although some protein subunits of complexes I and IV are encoded by mtDNA, most infant-onset isolated complex deficiencies probably are the result of autosomal-recessively inherited deficiency of nuclear-encoded respiratory chain subunits or of chaperone proteins that ensure proper assembly of functional complexes. For instance, hypertrophic cardiomyopathy caused by functional COX deficiency has been associated with mutations in nuclear COX subunit genes[30,31] or nuclear genes for COX associated-proteins SCO1 and SCO2.[32]

Cardiomyopathy may be seen in several other IEMs, but in these disorders, other physical or biochemical features are generally apparent at initial clinical presentation. For instance, dilated cardiomyopathy may complicate propionic acidemia during acute metabolic decompensation, but features of severe metabolic acidosis, vomiting, dehydration, coma, and possibly hyperammonemia are part of the initial clinical presentation.

Metabolic Myopathies and Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome resulting from skeletal muscle injury and release of potentially toxic substances into the circulatory system. Acute onset of severe muscle pain associated with increased serum CK levels is the hallmark of the disorder. In extreme cases, massive myoglobinuria may cause acute renal insufficiency. Although trauma and direct muscle injury are by far the most common causes of rhabdomyolysis, inborn errors of muscle metabolism should be considered in the differential diagnosis of rhabdomyolysis occurring at any age. In the absence of a history of trauma, the differential diagnosis of acute rhabdomyolysis should include drug or toxin exposure, muscle hypoxia (often associated with seizures), temperature alterations, inflammatory diseases, and IEMs. Because muscle contraction depends upon adenosine triphosphate (ATP) generated by the mitochondrial electron

transport chain, it follows that any process that impairs muscle ATP synthesis or which results in energy expenditure that surpasses ATP production could lead to rhabdomyolysis. The clinical history should lead toward the appropriate diagnosis. A family history that includes rhabdomyolysis or a history in which more than one episode of exercise-induced rhabdomyolysis has been observed should induce suspicion of a metabolic disorder. Along with muscular dystrophy and endocrine etiologies (hypothyroidism, hyperthyroidism, diabetic ketoacidosis, pheochromocytoma), glycolytic defects, fatty acid oxidation disorders, purine biosynthetic disorders, and disorders of mitochondrial oxidative phosphorylation should be considered if historical elements do not direct toward the more common etiologies. As described previously, the fatty acid oxidation disorders can be detected by urine organic acid analysis and plasma acylcarnitine profile. Chronic lactic acidosis may be a clue to a disorder of oxidative phosphorylation. Measurement of blood lactate level before and after an exercise treadmill protocol may help detect a respiratory chain defect if the postexercise lactate level is severely elevated. Definitive diagnosis of a mitochondrial disorder requires histologic and enzymatic analysis of a fresh muscle biopsy. The glycolytic defects of phosphofructokinase and phosphoglycerate mutase deficiencies along with myophosphorylase deficiency (glycogen storage disease type V or McArdle disease) cause severe recurrent rhabdomyolysis; their detection requires enzymatic analysis of muscle tissue. Likewise, myoadenylate deaminase deficiency, a defect in purine catabolism, and CPT-II deficiency are also diagnosed by measurement of the enzyme activities in muscle.

Neonatal Screening for Inborn Errors of Metabolism

Newborn screening for IEMs was first introduced in the 1960s, with screening for phenylketonuria. Technological advances, most significantly the introduction of tandem mass spectrometry to mass screening, have greatly increased the number of disorders that can be identified by analysis of a dried blood spot on a filter paper card.[33] An expert review conducted by the American College of Medical Genetics led to the recommendation that 29 core conditions, including several aminoacidopathies, fatty acid oxidation defects, and organic acidurias detectable by tandem mass spectrometry, should be included in the panel of disorders screened.[34] As of 2009, all states in the United States and most of Europe have now adopted this recommendation. The cost versus benefits of expanded screening, whether to include specific very rare or poorly treatable disorders in the screening panel, and the availability of adequate follow-up resources continue to be debated, but a general consensus has emerged that expanded newborn screening is an effective tool for identifying IEMs early in life, allowing for the initiation of therapy, often before the infant becomes symptomatic, and for preventing morbidity and mortality associated with IEMs.[35] It must be remembered, however, that newborn screening is just that—a screen, and both false-positive and false-negative results are possible. Thus the astute clinician must remain cognizant of the fact that in an ill infant, a normal newborn screen is reassuring but should not be taken as absolute proof-positive that an IEM identifiable on newborn screen is not present. Appropriate screening laboratory evaluation and emergency treatment should be instituted if clinical signs and symptoms of an IEM are present in a sick child.

Conclusion

Inborn errors of metabolism are individually rare but collectively will make not-infrequent appearances in a busy pediatric ICU. The signs and symptoms of IEMs may be nonspecific and often overlap extensively with more common disorders. When clinical suspicion of an IEM arises, screening biochemical genetic laboratory studies must be ordered. Further confirmatory testing often is necessary if screening laboratory tests point toward a specific disease. Confirmatory testing and disease-specific therapy should be instituted following consultation with a biochemical genetics specialist. If detected and treated early, the clinical outcome for many IEMs can be favorable.

References are available online at http://www.expertconsult.com.