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Articles

Clinical Approach to Genetic Cardiomyopathy in Children

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Abstract

Background Cardiomyopathy (CM) remains one of the leading cardiac causes of death in children, although in the majority of cases, the cause is unknown. To have an impact on morbidity and mortality, attention must shift to etiology-specific treatments. The diagnostic evaluation of children with CM of genetic origin is complicated by the large number of rare genetic causes, the broad range of clinical presentations, and the array of specialized diagnostic tests and biochemical assays.

Methods and Results We present a multidisciplinary diagnostic approach to pediatric CM of genetic etiology. We specify criteria for abnormal left ventricular systolic performance and structure that suggest CM based on established normal echocardiographic measurements and list other indications to consider an evaluation for CM. We provide a differential diagnosis of genetic conditions associated with CM, classified as inborn errors of metabolism, malformation syndromes, neuromuscular diseases, and familial isolated CM disorders. A diagnostic strategy is offered that is based on the clinical presentation: biochemical abnormalities, encephalopathy, dysmorphic features or multiple malformations, neuromuscular disease, apparently isolated CM, and pathological specimen findings. Adjunctive treatment measures are

recommended for severely ill patients in whom a metabolic cause of CM is suspected. A protocol is provided for the evaluation of moribund patients.

Conclusions In summary, we hope to assist pediatric cardiologists and other subspecialists in the evaluation of children with CM for a possible genetic cause using a presentation-based approach. This should increase the percentage of children with CM for whom a diagnosis can be established, with important implications for treatment, prognosis, and genetic counseling.

Key Words: diagnosis • genetics • cardiomyopathy

Introduction

Despite improvements in medical therapy and the increased availability of cardiac transplantation, CM remains one of the leading cardiac causes of death in children. The incidence of pediatric CM is not known because of a lack of clinical recognition and underreporting. In the majority of cases of pediatric CM, the cause is not identified and the prognosis is often grim. Recent studies [1 2 3 4](#) have shown that intensive palliative treatment does not lead to a better prognosis. A reduction in the morbidity and mortality associated with CM will require a better understanding of its causes and pathogenesis so that etiology-specific therapies can be implemented.

Children with CM may present with a variety of signs or symptoms, including congestive heart failure, arrhythmia, acute biochemical crisis, encephalopathy, generalized muscle weakness, dysmorphic features, and sudden death, or they may present with CM as an incidental finding during evaluation of an unrelated illness. Given the complex clinical presentations, the large number of rare associated disorders, and the array of diagnostic tests and biochemical assays, a thorough evaluation is usually most feasible at a center where advanced laboratory techniques and subspecialty support are available. A consistent, multidisciplinary approach to the diagnostic evaluation of such patients is needed. Several excellent reviews of pediatric CM have been published recently.[5 6 7 8 9](#) The purpose of the present report is to assist pediatric cardiologists and other subspecialists in the evaluation of patients with CM for a possible genetic cause using diagnostic algorithms based on the clinical presentation. We include disorders associated with a chromosomal abnormality or mutation of a nuclear or mitochondrial gene producing a mendelian or mitochondrial pattern of inheritance and exclude those with polygenic or multifactorial causes. While primary genetic causes of CM are being investigated, a broader differential diagnosis must also be considered (Table 1). A complete diagnostic evaluation should therefore

include the consideration of genetic and nongenetic conditions as dictated by clinical judgment in individual cases.

Table 1. Nongenetic Causes of CM*

Cardiovascular conditions
Atherosclerotic coronary artery disease
Kawasaki disease
Hypertension
Dysrhythmia
Congenital heart defect
Chronic alteration of circulatory volume
Cardiac transplantation
Major cardiac surgery or invasive cardiothoracic procedure within 1 month
Obesity
Pulmonary parenchymal or vascular disease
Pregnancy or the 3-month postpartum period
Infection
Toxin or drug
Radiation
Immunologic disease
Connective tissue disease
Endocrine disease, including disease in an infant of a diabetic mother
Nutritional deficiency
Granulomatous disease
Malignancy

*Although genetic factors play a part in several of these conditions, most are not genetic in the sense of being associated with single gene defects attributable to mendelian or mitochondrial inheritance or with a consistent chromosomal abnormality. Some listed conditions may have a primary genetic etiology, but CM is usually a secondary effect.

Criteria for Evaluation of CM

CM is broadly defined as a disease of the myocardium characterized by the presence of systolic or diastolic dysfunction or abnormal myocardial structure.^{10 11 12 13 14 15} The traditional classification of CM as dilated, hypertrophic, or restrictive is descriptive but

does not denote etiology. In several disorders, CM may be accurately classified as more than one type or may change from one type to another over time. In addition, the echocardiographic diagnosis of hypertrophic CM can include infiltrative disease as well as muscle hypertrophy, hyperplasia, interstitial edema, or fibrosis.

CM should be identified with the most appropriate tools to evaluate intrinsic myocardial abnormalities of systolic function (contractility), diastolic function (relaxation and compliance), and growth (hypertrophy and atrophy). Standardized, objective criteria for abnormal cardiac structure or function improve not only the accuracy of the diagnosis but also the understanding of the clinical course of CM. We have specified criteria for abnormal left ventricular systolic performance and structure in infants and children (Table 2) based on established normal echocardiographic measurements.¹⁶ The presence of any of these abnormalities should prompt an investigation of the cause, possibly including a diagnostic evaluation for CM. Any one of the criteria is consistent with CM, but the diagnosis is strengthened by the presence of two or more. We use left ventricular fractional shortening because it is a useful measurement of cardiac systolic function that is widely obtainable in children. Left ventricular fractional shortening is influenced by preload and afterload. Contractility measurements more accurately reflect the intrinsic health of the myocardium and, when available, are preferable for identifying CM.¹⁷

Table 2. Echocardiographic Indications of Abnormal Left Ventricular Function and Structure

Fractional shortening >2 SD below the normal mean value for age
Posterior wall thickness at end diastole >2 SD above the normal mean value for body surface area
Posterior wall thickness at end diastole >2 SD below the normal mean value for body surface area
End-diastolic (internal) dimension* >2 SD above the normal mean value for body surface area

*End-diastolic dimension=largest left ventricular dimension in short-axis view.

The ability to differentiate normal from abnormal parameters for several other, less well-defined aspects of cardiac structure and performance is limited. These parameters are continuously being revised as more is learned about the causes of CM. Examples of such indications that may warrant further evaluation for CM are listed in Table 3 .

Table 3. Additional Indications for Consideration of an Evaluation for CM

Isolated asymmetrical interventricular septal hypertrophy
Abnormalities of right ventricular structure or function (eg, parchment right ventricle or arrhythmogenic right ventricle)
Ventricular diastolic dysfunction (eg, restrictive CM)
Endocardial fibroelastosis
Arrhythmias or abnormal ECG findings

Differential Diagnosis of Genetic Disorders Associated With CM

Genetic conditions associated with CM can be classified into four categories, which are not mutually exclusive: inborn errors of metabolism, malformation syndromes, neuromuscular diseases, and familial isolated CM disorders. The largest group, inborn errors of metabolism, consists of infiltrative (storage) diseases, disorders of energy metabolism, and disorders that produce suspected cardiotoxic intermediary metabolites (Table 4).^{18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77} Malformation syndromes are recognizable patterns of minor and major anomalies that can often be attributed to a particular etiology (Table 5).^{78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115} Neuromuscular diseases affect the lower motor unit at the level of the peripheral nerve or skeletal muscle, and they frequently manifest as skeletal muscle weakness. This group includes muscular dystrophies, congenital myopathies, metabolic myopathies, and ataxias (Table 6).^{35 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130} Disorders of familial isolated CM (ie, CM without other features) include all three hemodynamic types, ie, hypertrophic, dilated, and restrictive, and can be associated with a variety of inheritance patterns (Table 7).^{23 24 51 52 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149}

Table 4. Inborn Errors of Metabolism Associated With CM

Infiltrative (storage)
Disorders of glycogen metabolism

Glycogen storage disease type II (Pompe disease: acid maltase deficiency) (H)18,19
Glycogen storage disease type III (Cori disease: debranching enzyme deficiency)(H)20,21*

Glycogen storage disease type IV (Andersen disease: branching enzyme deficiency)(D)22*

Glycogen storage disease type IX (cardiac phosphorylase kinase deficiency) (H)23,24*

Glycogen storage disease with normal acid maltase (H)25,26

Disorders of mucopolysaccharide degradation

Mucopolysaccharidosis type I (Hurler syndrome) (H, D)27,28
Mucopolysaccharidosis type II (Hunter syndrome) (H)29
Mucopolysaccharidosis type III (Sanfilippo syndrome) (H)29
Mucopolysaccharidosis type IV (Morquio syndrome) (H)29
Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) (D)30,31
Mucopolysaccharidosis type VII (Sly syndrome) (H)32

Disorder of glycosphingolipid degradation (Fabry disease) (H)33
Disorder of glucosylceramide degradation (Gaucher disease) (H)34
Disorder of phytanic acid oxidation (Refsum disease) (D, H)35

Disorders of combined ganglioside/mucopolysaccharide and oligosaccharide degradation

GM1 gangliosidosis (H, D)36,37
GM2 gangliosidosis (Sandhoff disease) (H, D)38

Disorder of glycoprotein metabolism

Carbohydrate-deficient glycoprotein syndrome (neonatal olivopontocerebellar syndrome)39
Disorder of oxalic acid metabolism (oxalosis)40

Diminished energy production

Disorders of pyruvate metabolism

Pyruvate dehydrogenase complex deficiency (Leigh disease) (H)41

Disorders of oxidative phosphorylation

Complex I deficiency (D)42
Complex II deficiency43
Complex III deficiency (histiocytoid CM) (H)44
Complex IV deficiency (muscle and Leigh disease forms) (H)45,46
Complex V deficiency (H)47,48

Combined respiratory chain deficiencies

Mitochondrial transfer RNA mutations

MELAS syndrome (H)49,50
MERRF syndrome (H, D)49
Others51-53

Mitochondrial DNA deletions and duplications

Kearns-Sayre syndrome (H)54

Others55

Barth syndrome (3-methylglutaconic aciduria type II) (H, D)56,57

Sengers syndrome (H)58,59

Others60

Disorders of fatty acid metabolism§

Primary or systemic carnitine deficiency (carnitine uptake deficiency) (H, D)61,62

Muscle carnitine deficiency (H, D)63,64

Carnitine palmitoyl transferase type II deficiency65

Carnitine acylcarnitine translocase deficiency66

Very-long-chain acyl-CoA dehydrogenase deficiency (H)67

Long-chain acyl-CoA dehydrogenase deficiency (H)68¶

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (D, H)69

Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency70

Multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia type II) (H)71

Toxic intermediary metabolites

Disorders of amino acid or organic acid metabolism

Propionic acidemia (D)72

Methylmalonic acidemia73

Malonic acidemia74

β-Ketothiolase deficiency (D)75

Mevalonic acidemia76

Tyrosinemia (H)77

Echocardiographic or pathological patterns are indicated for characterized diagnoses. H indicates hypertrophic CM; D, dilated CM; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Strokelike episodes; MERRF, Myoclonic Epilepsy, Ragged Red Fibers; and CoA, coenzyme A.

*Pathogenesis also includes diminished energy production.

Reported only in adults.

Questionable association or single case or family report.

§Pathogenesis also includes toxic metabolites.

¶Cases described in the literature are most likely very-long-chain acyl-CoA dehydrogenase deficiency.

Table 5. Malformation Syndromes Associated With CM*

Single gene or gene pair defect (mendelian disorder)

Autosomal dominant inheritance

Noonan syndrome (H)78,79

Cardio-facio-cutaneous syndrome (H)80

LEOPARD syndrome/lentiginosis/multiple lentigines (H)81,82

Neurofibromatosis (H)83

Beckwith-Wiedemann syndrome (H)84-86

Telecanthus, multiple congenital anomalies (H)87

Deaf-mutism (H)88

Rubinstein-Taybi syndrome (H)89

Autosomal recessive inheritance

Hypogonadism, multiple congenital anomalies, mental retardation (D)90

Microcephaly, mental retardation (D)91

Palmoplantar keratosis (D)92

Total lipodystrophy, insulin resistance, leprechaunism (H)93

Costello syndrome (H)94

Macrosomia, postnatal growth and mental retardation, Costello-like features95

Mental retardation, unusual facies, arthritis, deafness96

Facio-cardio-renal syndrome97

Genitourinary anomalies, mental retardation98

Alstrom syndrome (D)99

Marden-Walker syndrome100

Short-limbed dwarfism101

Leber congenital amaurosis102

X-linked recessive inheritance

Cutis laxa, skeletal abnormalities (H)103

Microphthalmos, linear skin defects (H, D)104

Simpson-Golabi-Behmel-Rosen syndrome105,106

Mental retardation, precocious puberty, obesity103

Chromosome defect

Deletion 2q23 (A.E.L. and R.V.L., unpublished data, 1993)

Deletion 10q25 mosaicism (A.E.L., unpublished data, 1988)

Deletion 11p15 with aniridia, catalase deficiency107

Duplication 9p22 (A.E.L., unpublished data, 1993)

Unknown genesis syndrome

Ectodermal dysplasia, hypothyroidism, agenesis corpus callosum, mental retardation108

Mental retardation, multiple congenital anomalies, neurological dysfunction109

Cataracts, arthropathy110

Absent ulna and radius¹¹¹
 Hidrotic ectodermal dysplasia¹¹²
 Hypogonadism, collagenomas¹¹³
 Mental retardation, craniosynostosis, multiple congenital anomalies¹¹⁴
 Proteus syndrome¹¹⁵

Echocardiographic or pathological patterns are indicated for characterized diagnoses. H indicates hypertrophic CM; D, dilated CM; and LEOPARD, Lentiginos, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, and Deafness.

*Includes reports with unspecified type of CM, clinically diagnosed CM without imaging or postmortem confirmation, parchment right ventricle, and endomyocardial fibroelastosis. Excluded are reports of nonspecific cardiomegaly, myocardial necrosis, or isolated ECG abnormalities.

Questionable association or single case report.

Table 6. Neuromuscular Disorders Associated With CM

Muscular dystrophies
DMD (D) ^{116,117}
BMD (D) ¹¹⁸
Autosomal recessive muscular dystrophy (D) ¹¹⁹
Myotonic dystrophy (H, D) ¹²⁰
Emery-Dreifuss muscular dystrophy (D) ^{121,122}
Limb-girdle muscular dystrophy (D) ¹²³
Congenital muscular dystrophy ^{123a}
Congenital myopathies
Centronuclear (myotubular) myopathy (D) ¹²⁴
Nemaline rod myopathy (D, H) ^{125,126}
Minicore-multicore myopathy (D, H, R) ^{127,128}
Metabolic myopathies*
Ataxias
Friedreich ataxia (H) ^{129,130}
Refsum disease (D, H) ³⁵

Echocardiographic or pathological patterns are indicated for characterized diagnoses. H indicates hypertrophic CM; D, dilated CM; and R, restrictive CM.

*Listed in Table 3.

Table 7. Isolated CM

Autosomal dominant inheritance
Familial hypertrophic CM131
Defect in cardiac myosin β heavy chain (linkage to chromosome 14q11-q12)132,133
Defect in cardiac troponin T (linkage to chromosome 1q3)134
Defects in α -tropomyosin (linkage to chromosome 15q2)134
Defect in cardiac myosin binding protein-C (linkage to chromosome 11p11.2)135
Linkage to chromosome 7q3 with Wolff-Parkinson-White syndrome136
Familial CM with multiple mitochondrial DNA deletions (D)137
Familial dilated CM linked to chromosome 1p138
Familial restrictive CM139,140
Parchment right ventricle and arrhythmogenic right ventricle141-143
Noncompaction of the left ventricle144
X-linked inheritance
Dilated CM (defect in dystrophin)145-147
Autosomal recessive inheritance*
Cardiac phosphorylase kinase deficiency (H)23,24
Familial dilated CM148
Familial hypertrophic CM149
Maternal (mitochondrial) inheritance
C3303T tRNA Leu51
T9997C tRNA Gly52
Sporadic
Any of the above

Echocardiographic or pathological patterns are indicated for characterized diagnoses. H indicates hypertrophic CM; D, dilated CM.

*Some apparently autosomal recessive defects may actually be autosomal dominant in which one parent is a mosaic or has incomplete expression.

Diagnostic Approach Based on Clinical Presentation

There are very few pathognomonic cardiac features associated with CM, such as the ECG finding of a short PR interval with huge QRS voltages characteristic of Pompe disease. For this reason, other associated physical or laboratory findings are needed to help focus the diagnostic evaluation. Patients with inborn errors of metabolism

involving impaired energy production or the accumulation of toxic metabolites often have signs and symptoms of multiple organ dysfunction. When the demand for energy greatly exceeds available energy stores (eg, during illness, physical stress, or decreased oral intake), patients with impaired energy metabolism are unable to maintain homeostasis, which may lead to hypoglycemia, metabolic acidosis, and/or hyperammonemia. Indications to screen for a biochemical abnormality include acute or chronic encephalopathy, muscle weakness, hypotonia, growth retardation, failure to thrive, recurrent vomiting, and lethargy. In contrast, patients with storage diseases who cannot degrade certain structural components of cells typically develop coarse or dysmorphic facial features, organomegaly, skeletal deformities, short stature, or chronic encephalopathy associated with a neurodegenerative course. Dysmorphic features may characterize malformation syndromes as well as storage diseases, and therefore other minor and major malformations should also be sought. Skeletal muscle weakness without encephalopathy, although sometimes due to a disorder of energy metabolism, may also indicate a primary neuromuscular disorder. In these patients, skeletal muscle weakness usually precedes CM and dominates the clinical picture. Occasionally, however, skeletal myopathy is subtle, and the first symptom of disease may be cardiac failure. The absence of associated physical or biochemical abnormalities at presentation may signify an isolated familial CM disorder or possibly the early manifestation of a multisystem disease that warrants investigation. Although in most cases, isolated CM is clinically and pathologically nonspecific and consequently is considered idiopathic, the identification of specific DNA mutations and protein abnormalities for some of these cases now provides a basis for etiologic differentiation. Endomyocardial biopsy may narrow the genetic differential diagnosis or provide evidence for a nongenetic cause. Occasionally, clinically unsuspected CM is diagnosed at autopsy. The following major physical findings and laboratory results associated with CM may guide the clinical evaluation.

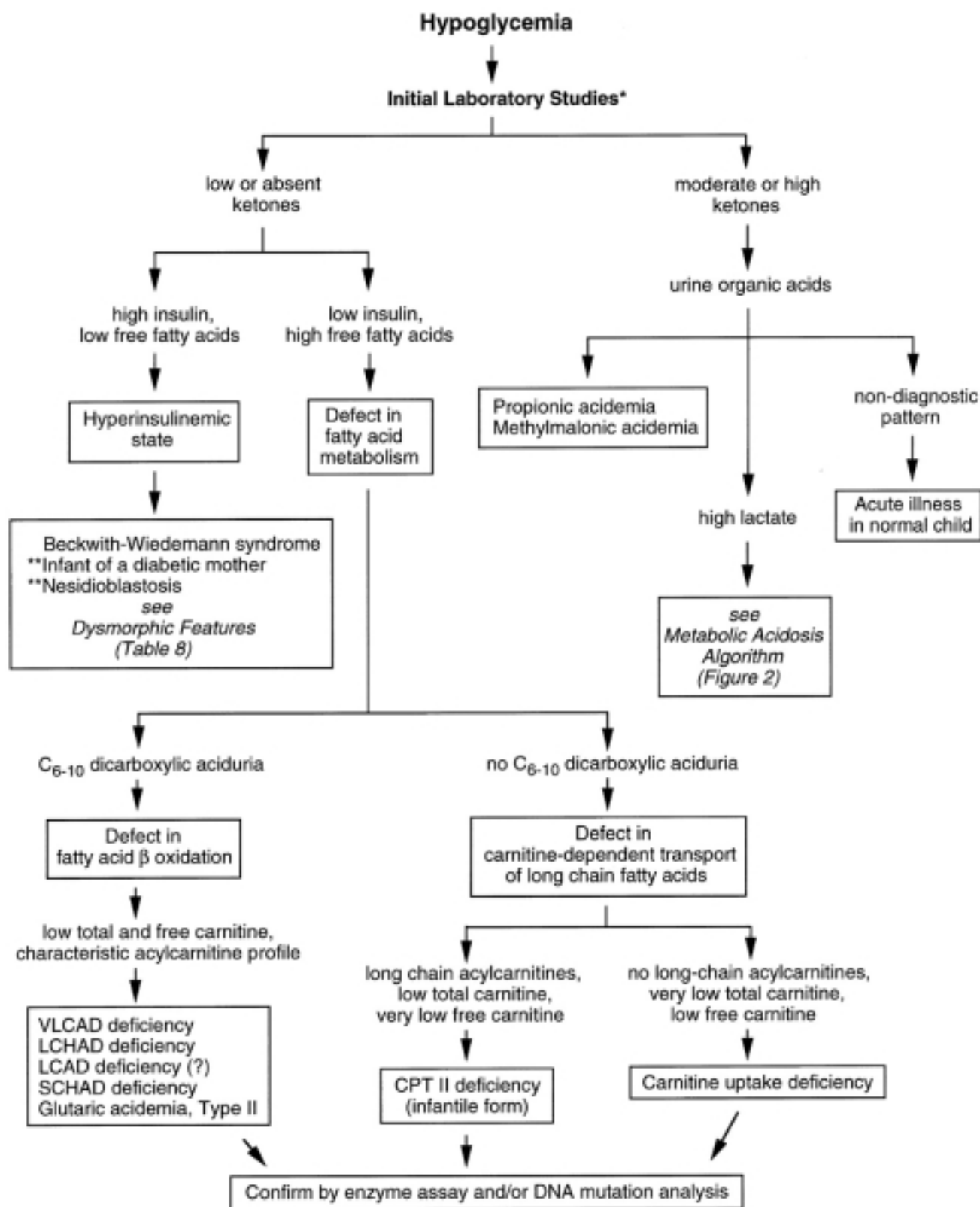
Biochemical Abnormalities

Because many of the clinical features of disorders of intermediary metabolism are nonspecific, the diagnosis usually depends on the results of laboratory tests that are most diagnostic when performed during the acute phase of illness. The presence of hypoglycemia, primary metabolic acidosis with an increased anion gap, or hyperammonemia should alert the physician to the possibility of a metabolic disorder. It is important to obtain blood and urine specimens as soon as possible after presentation, because the diagnostic compounds may become diluted or their production diminished once treatment has begun. The initial laboratory studies should be used to try to determine which metabolic pathway(s) is the most likely site of a biochemical defect. Additional plasma and urine should be collected and frozen for further specialized testing. Normal infants and young children may become

hypoglycemic, ketotic, and/or acidotic in response to decreased oral intake during a severe illness. Hypoketotic hypoglycemia (Fig 1) is a distinctly abnormal response and is the hallmark of a defect in fatty acid metabolism. Hyperketotic hypoglycemia is characteristic of defects in organic acid metabolism. However, the presence of ketones is nonspecific and can be associated with a high lactate level.

Adf adf

Figure 1. Algorithm for CM associated with hypoglycemia. With hypoketotic hypoglycemia due to a defect in fatty acid metabolism, free fatty acid levels are high and insulin levels are low. The insulin-excess states of Beckwith-Wiedemann syndrome, the infant of a diabetic mother, and nesidioblastosis can also produce hypoketotic hypoglycemia but are distinguished by low free fatty acid levels and characteristic clinical features. Disorders in fatty acid metabolism can be further identified as defects of fatty acid β -oxidation or of carnitine-dependent transport depending on quantitative carnitine levels in blood, urine, and tissue; acylcarnitine profile in blood; and urine organic acids (fatty acids, dicarboxylic, and hydroxydicarboxylic acids). VLCAD indicates very-long-chain acyl coenzyme A dehydrogenase deficiency; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LCAD, long-chain acyl-CoA dehydrogenase deficiency; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; CPT, carnitine palmitoyl transferase type II deficiency; CBC, complete blood count; AST, aspartate aminotransferase; ALT, alkaline aminotransferase; and CK, creatine kinase.

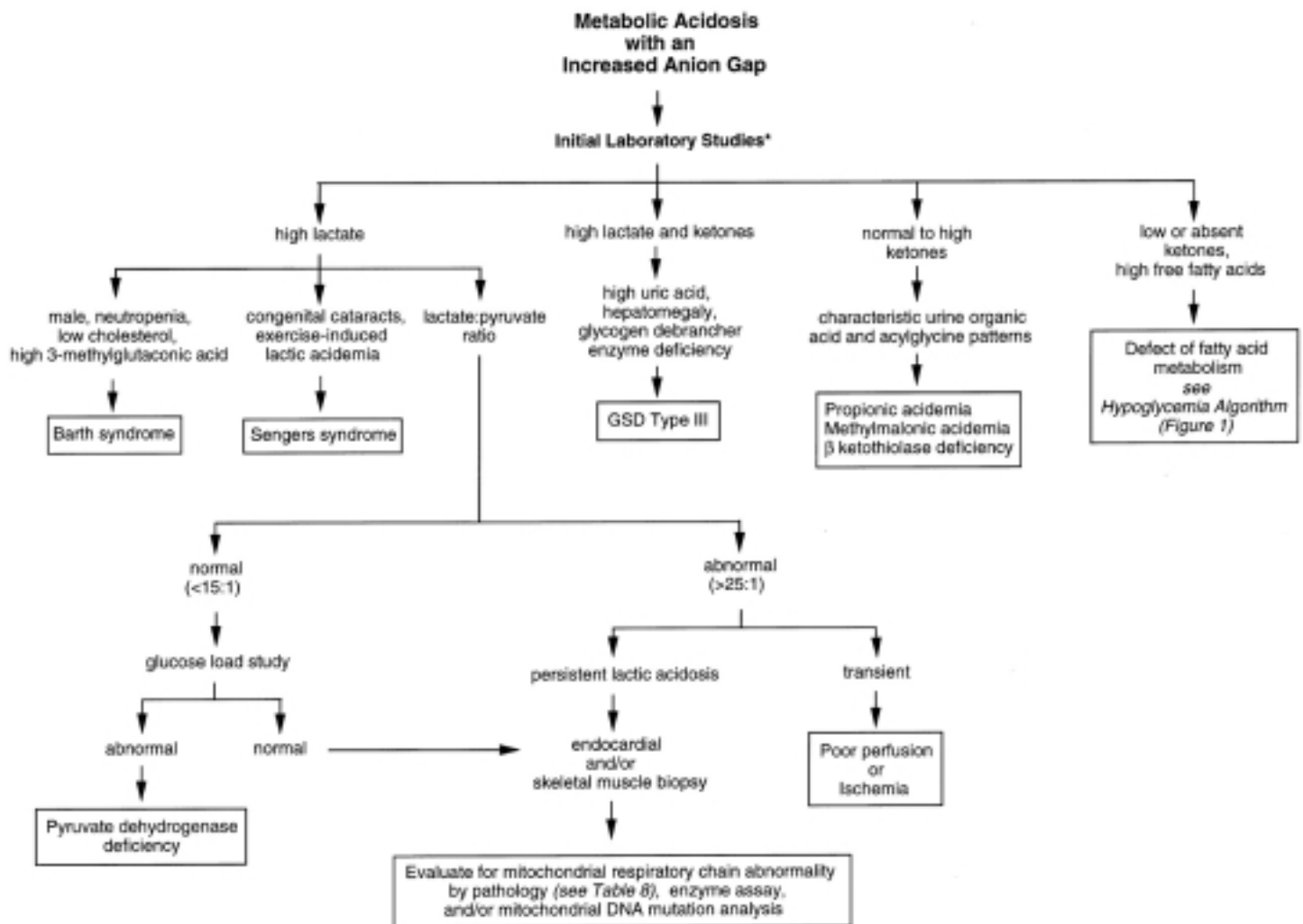


*Blood: electrolytes, BUN, creatinine, glucose, pH, ammonia, CBC with differential, lactate, pyruvate, AST, ALT, bilirubin, CK, uric acid, cholesterol, triglycerides, insulin, ketones, free fatty acids, amino acids, carnitine, and acylcarnitine filter paper spot. Freeze 3 ml plasma for further studies.
Urine: urinalysis, organic acids, amino acids, and acylglycine. Freeze 20 ml for further studies.

**Non-genetic differential diagnosis

When metabolic acidosis with an increased anion gap is present (Fig 2), the identification of the organic acid(s) in urine and/or blood responsible for the increased anion gap is often the key to the diagnosis. The principal metabolites of concern are free fatty acids, ketoacids, dicarboxylic acids, lactate, and pyruvate. When possible, specific diagnoses should be confirmed by enzyme assay or DNA mutation analysis.

Figure 2. Algorithm for CM associated with metabolic acidosis. High levels of plasma free fatty acids with low to absent ketone levels likely indicate a defect of fatty acid metabolism. Propionic and methylmalonic acidemias are associated with high ketone levels. Lactate is the predominant organic acid in glycogen storage disease (GSD) type III, Barth syndrome, Sengers syndrome, pyruvate dehydrogenase complex deficiency, and some defects of oxidative phosphorylation. The first three of these diagnoses are distinguished by their characteristic clinical and laboratory findings. The latter two diagnoses can be differentiated by the lactate:pyruvate ratio. 3-Methylglutaconic acid can be measured in plasma or by urine organic acid analysis. Abbreviations as in Fig 1.



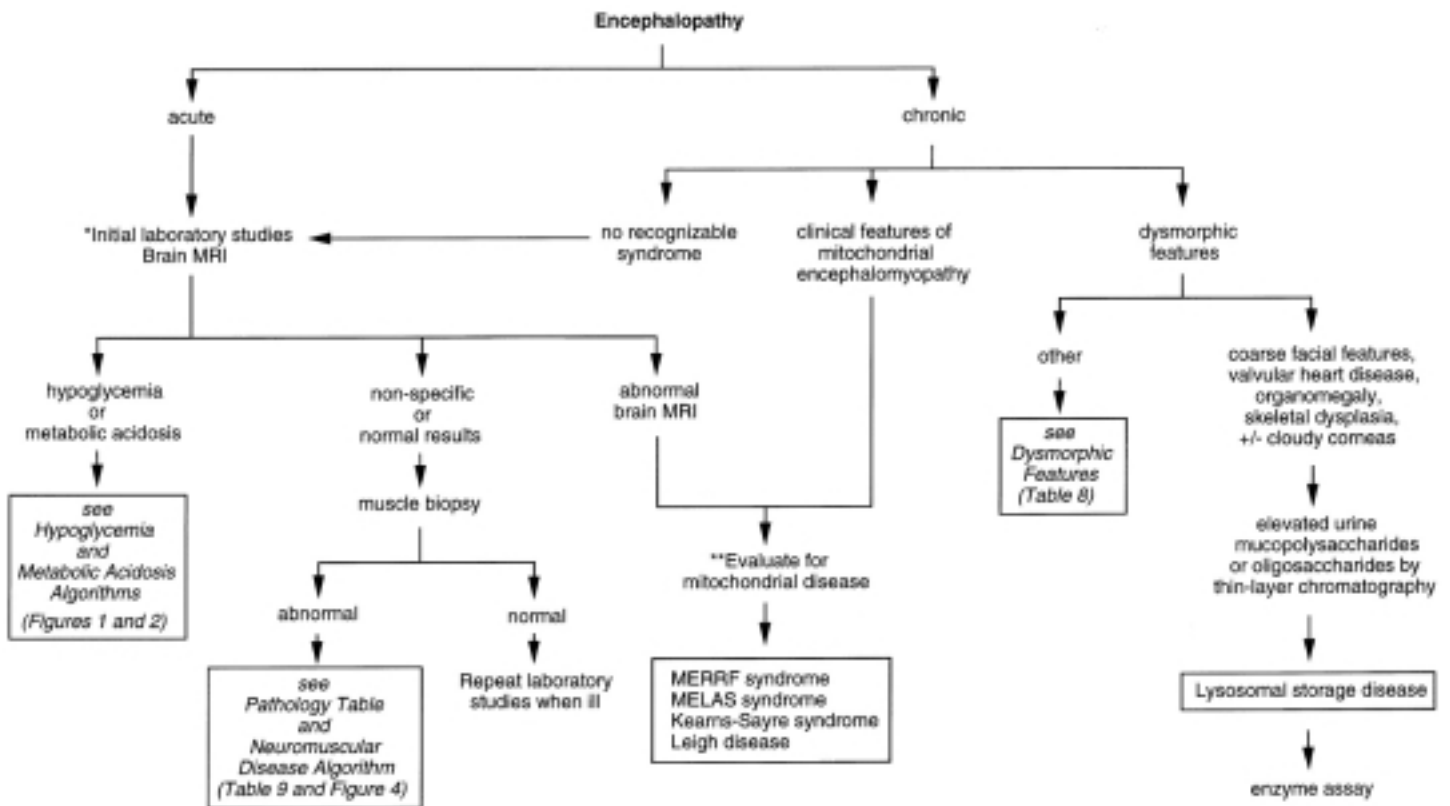
*Blood: electrolytes, BUN, creatinine, glucose, pH, ammonia, CBC with differential, lactate, pyruvate, AST, ALT, bilirubin, CK, uric acid, cholesterol, triglycerides, free fatty acids, ketones, amino acids, carnitine, filter paper spot for acylcarnitine. Freeze 3 ml plasma for further studies. Urine: urinalysis, organic acids, amino acids, acylglycine. Freeze 20 ml for further studies.

Specialized laboratory testing may be necessary to identify the metabolites that are diagnostic of a particular inborn error of metabolism. These tests include plasma acylcarnitine profile by fast atom-bombardment tandem mass spectrometry and urinary acylglycine analysis by stable isotope dilution and gas chromatography–mass spectrometry. These tests frequently can detect low levels of diagnostic metabolites in asymptomatic patients who have no gross biochemical changes in their blood or urine, thereby making evaluation possible in the outpatient setting. Once a pattern of diagnostic metabolites has been identified, certain in vivo tests that may be useful to confirm the diagnosis or to evaluate the benefits of therapy include glucose loading for pyruvate dehydrogenase complex deficiency, medium- and long-chain triglyceride loading for fatty acid oxidation defects, and carnitine loading for systemic carnitine deficiency. These tests should be performed by metabolism specialists under closely monitored conditions, because they may precipitate an acute metabolic crisis and consequently are potentially dangerous.

Encephalopathy

Encephalopathy, broadly defined as any alteration in brain function that leads to impaired mental status, developmental delay, coma, seizures, apnea, autonomic dysfunction, dystonia, or strokelike episodes, can be an important discriminating clinical feature in the evaluation of CM (Fig 3). Acute encephalopathy frequently occurs during a metabolic decompensation, and biochemical abnormalities should be sought. (See "Biochemical Abnormalities.") The mechanisms for biochemical encephalopathy, although only partially understood, probably include a combination of acute and chronic energy deprivation in the brain and an accumulation of toxic intermediate metabolites.

Figure 3. Algorithm for CM associated with encephalopathy. MRI indicates magnetic resonance imaging; MERRF, Myoclonic Epilepsy, Ragged Red Fibers; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Strokelike episodes; and CSF, cerebrospinal fluid. Other abbreviations as in Fig 1 .



***Initial laboratory studies:**

Blood: electrolytes, BUN, creatinine, glucose, pH, ammonia, CBC with differential, lactate, pyruvate, AST, ALT, bilirubin, CK, uric acid, free fatty acids, ketones, cholesterol, triglyceride, amino acids, carnitine, and acylcarnitines
 Freeze 5 ml plasma.
 Urine: urinalysis, organic acids, amino acids, and acylglycines
 Freeze 20 ml urine.
 CSF: lactate, pyruvate, cell count, protein, glucose, and amino acids

****Mitochondrial disease laboratory studies:**

Blood: lactate, pyruvate, amino acids, and DNA for mitochondrial DNA point mutation analysis
 Urine: amino acids and organic acids
 CSF: lactate, pyruvate, cell count, protein, glucose, and amino acids
 Muscle biopsy for light and electron microscopy, respiratory chain enzyme assay, and mitochondrial DNA deletion and point mutation analysis

Chronic encephalopathy is characteristically seen in the mitochondrial syndromes MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Strokeliike episodes), MERRF (Myoclonic Epilepsy, Ragged Red Fibers), Kearns-Sayre syndrome, and Leigh disease. Acute worsening can occur in these syndromes in association with intercurrent illness or metabolic stressors. In general, the neurological features of these syndromes (epilepsy, strokelike episodes, dementia, and ophthalmoplegia) predominate, and CM typically occurs later in the clinical course. The diagnosis is based on measurement of blood and cerebrospinal fluid lactate and pyruvate levels, histological analysis of skeletal muscle, assay of respiratory chain enzymes, and/or mitochondrial DNA analysis. A neurodevelopmental decline associated with valvar heart disease, coarse facies, organomegaly, skeletal deformities, or cloudy corneas

suggests the possibility of an underlying lysosomal storage disease such as a mucopolysaccharidosis or mucopolipidosis.

Dysmorphic Features

CM is uncommon in malformation syndromes and is usually reported in small patient series or as isolated cases. Occasionally, the constellation of CM with major and minor anomalies constitutes a recognizable syndrome, but often a specific syndrome is not identified. Noonan syndrome is the most familiar syndrome associated with CM. Patients with this disorder usually have a characteristic facies (hypertelorism, ptosis, epicanthal folds, and external ear anomalies), neck webbing, pectus abnormalities, and pulmonary stenosis. Left ventricular hypertrophy is common (10% to 20%),^{78 79 150} but biventricular involvement can be seen. Onset of CM in infancy or childhood is typical. Most affected children have asymptomatic CM, although severe presentation in infants has been reported.¹⁵¹

Hypertrophic CM has been reported less frequently in several disorders with clinical features overlapping those of Noonan syndrome: cardio-facial-cutaneous syndrome, neurofibromatosis type I, multiple lentigines (lentiginosis), and LEOPARD syndrome (Lentigines, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, and Deafness).^{80 81 82 83 152} Whether these are distinct or allelic genetic defects continues to be investigated.¹⁵³

Although the distinctive phenotype in Noonan syndrome is familiar to many pediatricians, most of the other syndromes associated with CM are rare. Table 8 presents distinctive anomalies found in several of these syndromes. Nonspecific dysmorphic features, such as epicanthal folds, hypertelorism, and low-set ears, are omitted. In severely hypotonic children with neuromuscular diseases, certain nonspecific dysmorphic features are often due to hypotonia itself, such as an open mouth with protruding tongue, midface flattening, and ptosis. The facial coarsening that invariably accompanies many storage diseases is an acquired abnormality. Because some findings may be subtle, the patient with CM should be evaluated formally for anomalies, including an ophthalmologic examination and often a chromosomal analysis.

Table 8. Dysmorphic Features Found in Malformation Syndromes and Other Genetic Disorders Associated with CM*

Organ System	Feature	Syndrome
Growth	Short stature	Noonan syndrome

<p>Skeleton</p>	<p>Macrosomia/overgrowth</p> <p>Joint laxity</p>	<p>Multiple lentigines Mucopolysaccharidoses Beckwith-Wiedemann syndrome Costello syndrome Cutis laxa, skeletal anomalies syndrome</p>
<p>Skin/hair</p>	<p>Pectus Kyphoscoliosis Wiry hair</p> <p>Palmar keratosis</p> <p>Lentigines Cafe au lait spots</p> <p>Neurofibromas Cutis laxa/loose skin Deep plantar furrows Linear skin defects</p>	<p>Noonan syndrome Mucopolysaccharidoses Cardio-facio-cutaneous syndrome Cardio-facio-cutaneous syndrome Palmoplantar keratosis Multiple lentigines Neurofibromatosis, type 1 Noonan syndrome Neurofibromatosis, type 1 Costello syndrome Costello syndrome Microphthalmos with linear skin defects</p>
<p>Facies</p>	<p>Lipodystrophy</p> <p>Distinctive</p> <p>Coarse</p>	<p>Lipodystrophy, insulin resistance, leprechaunism Noonan syndrome Cardio-facio-cutaneous syndrome</p>
<p>Other craniofacial</p>	<p>Nonspecific hypotonia Telecanthus Cataracts</p> <p>Nystagmus Macroglossia</p>	<p>Mucopolysaccharidoses Pompe disease Inborn error of metabolism Neuromuscular disease Telecanthus, MCA syndrome Sengers syndrome Leber congenital amaurosis Leber congenital amaurosis Beckwith-Wiedemann syndrome Pompe disease</p>
<p>Central nervous system</p>	<p>Ear creases Neck webbing Microcephaly</p>	<p>Beckwith-Wiedemann syndrome Noonan syndrome Microcephaly, MR syndrome</p>

External genitalia	Contractures Hypogonadism Cryptorchism Genital anomalies	Marden-Walker syndrome Hypogonadism, MCA, MR syndrome Hypogonadism, collagenoma syndrome Alstrom-like syndrome with hypogonadism Noonan syndrome Genitourinary anomalies, MR syndrome
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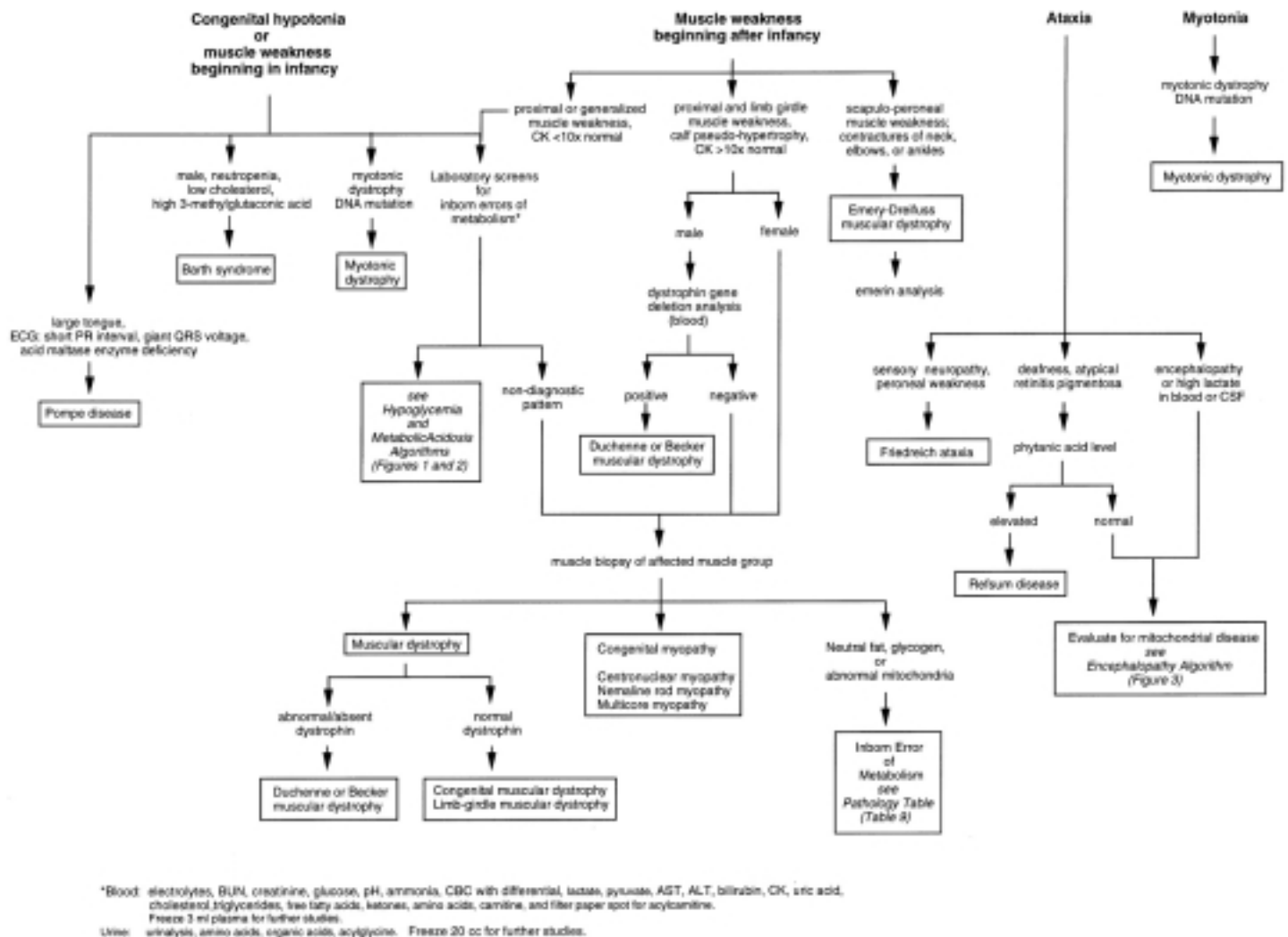
MCA indicates multiple congenital anomalies; MR, mental retardation.

*Only distinctive clinical features and diagnoses clearly associated with CM are listed.

Neuromuscular Disease

Four clinical presentations that serve as useful starting points for the diagnostic algorithm for neuromuscular diseases associated with CM are congenital hypotonia or weakness (floppy infant syndrome), weakness beginning after infancy (>1 year of age), ataxia (loss of motor control), and myotonia (decreased muscle relaxation) (Fig 4). Additional findings that support the diagnosis of a neuromuscular disease include a distinct pattern of muscle weakness, decreased muscle bulk, decreased or absent deep tendon reflexes, elevated serum creatine kinase levels, and an abnormal nerve conduction velocity or electromyogram. Although these clinical signs and laboratory tests are useful for identifying and classifying diseases of the lower motor unit, in isolation, they rarely lead to a specific diagnosis. However, certain generalizations can be made. A markedly elevated serum creatine kinase level (10 to 100 times higher than normal) is invariably found early in the clinical course of DMD and almost always in its milder allelic form, BMD, whereas the serum creatine kinase level is usually lower in other muscular dystrophies and myopathies (1 to 10 times higher than normal). Because creatine kinase levels can vary markedly among different patients with the same disease and may fluctuate in a given patient over time, clinical judgment is necessary to interpret these values. Nerve conduction velocity and electromyography are useful for detecting myotonia and distinguishing peripheral neuropathy from myopathy, but the results can be difficult to interpret in newborns and young infants, and mild disease might not be detected.

Figure 4. Algorithm for CM associated with neuromuscular disease. CSF indicates cerebrospinal fluid. Other abbreviations as in Fig 1 .



When CM is associated with hypotonia or weakness in a newborn or older infant, the most likely genetic cause is an inborn error of metabolism or a congenital myopathy. CM associated with inborn errors of metabolism usually occurs early in the clinical course and is the predominant clinical finding, whereas skeletal muscle weakness or hypotonia is the most prominent initial manifestation of the congenital myopathies.

Cardioskeletal myopathy beginning after infancy may be categorized initially according to the pattern of skeletal muscle involvement: proximal muscle weakness (DMD, BMD, and limb-girdle muscular dystrophies), scapulo-peroneal weakness (Emery-Dreifuss muscular dystrophy), and generalized weakness (later onset forms of inborn errors of metabolism and congenital myopathies). DMD and BMD are associated with calf

pseudohypertrophy, whereas Emery-Dreifuss muscular dystrophy is characterized by neck and limb contractures that precede muscle weakness. In DMD and BMD, CM usually develops insidiously over several years after skeletal muscle weakness is well established. Scarring of the posterobasal left ventricular wall leads to characteristic ECG changes (an anterior shift of the QRS complex, with tall R waves in the right precordial leads and deep, narrow Q waves in leads I and aVL and the left precordial leads).^{117 154 155 156} Heart block and sudden death are additional cardiac findings in Emery-Dreifuss and myotonic muscular dystrophies.^{122 157}

Ataxia associated with CM is prominent in Refsum disease, Friedreich ataxia, and mitochondrial encephalomyopathies. Only Friedreich ataxia is consistently associated with CM.^{128 129} Although commonly associated with CM in adults, myotonic dystrophy has been reported only rarely with CM in children.¹²⁰

A skeletal muscle biopsy is often necessary, especially in infants, when the clinical and laboratory findings are nonspecific. If a muscular dystrophy is suspected, particularly in a boy, molecular analysis of the dystrophin gene and/or protein is indicated. Dystrophin, a cytoskeletal protein normally found in all muscle cell types, is thought to stabilize the plasma membrane of the muscle cell and may be important in the regulation of intracellular calcium.¹¹⁶ Approximately 65% of patients with DMD or BMD have deletions of the dystrophin gene that can be detected by PCR in blood lymphocytes.^{158 159} In the other 35% of patients, including manifesting female carriers for whom PCR results are difficult to interpret, a muscle biopsy is required to detect a reduced amount of the dystrophin protein or abnormalities of its size.^{160 161 162 163} The presence of dystrophic changes in a skeletal muscle biopsy specimen is also an indication for molecular analysis of dystrophin. ARMD, which is clinically and pathologically similar to BMD and DMD, has been in one case associated with a deficiency of a dystrophin-associated glycoprotein. When muscle analysis for dystrophin is normal in a patient in whom BMD or DMD is suspected, muscle should be further analyzed for a defect of the dystrophin-associated glycoprotein complex.¹¹⁹

CM Without Other Abnormalities

If a patient presents with CM and no apparent associated physical or laboratory abnormality that would lead to one of the diagnoses discussed above, an isolated CM should be considered. However, the clinician should be aware that extracardiac manifestations of some genetic disorders may be subtle, especially early in life, or may develop over time. Therefore, it is important to evaluate the patient and immediate family members for these findings. Although many diagnoses can be elucidated by a thorough initial investigation, repetition of studies is often necessary during times of metabolic stress or during closely monitored inpatient fasting conditions.

The patient's age at presentation of CM can guide the investigation. When an infant presents with apparently isolated CM, a careful dysmorphology evaluation should be performed, including an ophthalmologic examination for cataracts. Screening metabolic laboratory studies may give evidence of a mitochondrial, fatty acid oxidation, or glycogen storage disease. If the results of these studies are normal, an endomyocardial biopsy should be sent for pathological analysis. Cardiac phosphorylase kinase deficiency, a rare cause of isolated CM in the young infant, can be diagnosed only in this way. Biopsy findings may suggest specific enzyme assays that may be more easily performed on other tissues. A similar evaluation should be performed for children with apparently isolated CM. In addition, congenital myopathy, although usually manifest in early infancy, may present later in childhood. Adolescent patients may develop apparently isolated CM in association with BMD or ARMD. In rare cases, the skeletal myopathy of BMD or ARMD may be very subtle or even absent, so that CM is the only apparent clinical feature. Nevertheless, serum levels of creatine kinase are often elevated in these patients.^{118 119 164} Muscle should be analyzed in these patients for a defect in dystrophin and/or dystrophin-associated glycoprotein complex.

When no extracardiac findings are identified and there is a family history of isolated CM through successive generations, familial isolated CM is likely. Several forms of familial isolated CM have been described according to the myocardial structure and the mode of inheritance (Table 6).

The best delineated form of isolated CM is familial hypertrophic CM, a primary myocardial disease often caused by abnormalities of various contractile proteins.^{132 133 134} Unexplained nondilated, often hypercontractile left ventricular myocardial hypertrophy in the absence of systemic or intracardiac disease is a fundamental abnormality.¹⁶⁵ Although asymmetrical septal hypertrophy with relative sparing of the posterior left ventricular free wall is the classic and most common pattern of familial hypertrophic CM, it is not found universally.^{166 167 168 169 170 171} Careful echocardiographic evaluation of relatives has shown that the rate of familial hypertrophic CM is 55%, with an autosomal dominant pattern of inheritance in 77% of affected families.¹⁷² Therefore, when isolated hypertrophic CM is diagnosed, echocardiograms and ECGs should be performed on first-degree relatives and any family members with possible cardiac symptoms to identify subclinical cases. Maximal left ventricular wall thickness may be significantly different between kindreds and therefore should be assessed in the context of the cardiac dimensions of family members. Also, disease expression may vary within a family. When there is no

echocardiographic evidence of ventricular hypertrophy, an ECG showing myocardial ischemia may identify family members at risk.¹⁷³ However, an index case may result from a new mutation or recessive inheritance. Although clinical presentation in infants and children is uncommon, the incidence of sudden death is considerably higher in this age group than in older children.^{174 175} Children are usually asymptomatic at presentation but rarely may present with symptoms of early dynamic obstruction of the left ventricular outflow tract (eg, exercise intolerance or shortness of breath). Adolescents tend to present with chest pain possibly due to myocardial ischemia. Syncope as a presenting symptom is rare and signifies a poor prognosis.¹⁷⁶

Similar to familial hypertrophic CM, familial dilated CM may be caused by multiple genes and exhibit considerable phenotypic variability. Although most cases of dilated CM are thought to be sporadic, the frequency of familial cases of apparently idiopathic dilated CM has been reported to be {approx} 20%.^{148 177} Like DMD and BMD, some cases of X-linked dilated CM have been attributed to a defect in the dystrophin gene. In X-linked dilated CM, the defect in dystrophin is manifested only in cardiac myocytes.¹⁷⁸ Male patients with X-linked dilated CM are usually asymptomatic in childhood and present with syncope and rapidly progressive congestive heart failure in their teens or early 20s (to be distinguished from Barth syndrome, an X-linked cardioskeletal myopathy with neutropenia, which usually presents in infancy and is due to a defect in a distinct gene on Xq28). Female patients have atypical chest pain in their fourth decade with a gradual progression to congestive heart failure over several years.¹⁴⁶ Similarly, female carriers of DMD may have isolated dilated CM as the only manifestation of the disease.¹⁶⁰ It has been suggested that dystrophin protein analyses should be performed with cardiac and skeletal muscle biopsies in patients with idiopathic dilated CM when the family history is negative for muscular dystrophy.^{160 161 162 179 180 181}

Pathological Findings

Many centers have reported ^{182 183 184 185} that endomyocardial biopsies provide significant diagnostic information in cases of apparently idiopathic CM and can be performed safely in children. Table 9 lists the important light or electron microscopic features observed in endomyocardial biopsy specimens, as well as the diseases in which these findings are characteristic or sometimes encountered. Histological features seen only in nongenetic diseases are also listed. Some of the features are specific for a particular group of disorders (eg, glycogen storage diseases) or for a particular disease (eg, Fabry disease). The presence of endomyocardial fibroelastosis, although nonspecific, usually indicates a poor prognosis.¹⁸⁶ In addition, tissues other than the endomyocardium are frequently used to diagnose some disorders, particularly

storage and mitochondrial diseases and those characterized by the accumulation of neutral fat (eg, skeletal muscle, liver, and occasionally skin). An exception is cardiac phosphorylase kinase deficiency, which can be diagnosed only from cardiac tissue.

Table 9. Pathological Findings in CM

Storage
Glycogenosis
Free glycogen: types III, IX
Both free and intralysosomal glycogen: type II Pompe disease
Amylopectin: type IV, polysaccharidosis
Glycoproteins
Fucosidosis, type I
Mannosidosis
Sphingolipidosis
Fabry disease
Mucopolysaccharidosis (type I, II, III, IV, VI)
GM1 and GM2 gangliosidosis
Gaucher disease
Oxalosis
Nemaline myopathy
Masses of intermediate filaments (desmin)
Sarcoplasmic neutral fat
Systemic carnitine deficiency
Long-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Carnitine palmitoyl transferase type II deficiency
Multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia type II)
Barth syndrome
Sengers syndrome
Refsum disease
Abnormal mitochondria (structural and/or numerical)
Mitochondrial respiratory chain defects
Complex IV deficiency
Leigh disease
Friedreich ataxia
Kearns-Sayre syndrome
MELAS syndrome
MERRF syndrome
Barth syndrome
Sengers syndrome

Infantile histiocytoid "oncocytic" CM
Left ventricular noncompaction
Systemic carnitine deficiency
Nonspecific changes
Endocardial fibroelastosis
Nuclear enlargement, hyperchromatism, and polymorphism
Hypertrophy
Beckwith-Wiedemann syndrome
Interstitial fibrosis
Mild mitochondrial changes in number and morphology
Alterations in sarcomere organization, myofilament loss, accumulation of residual bodies
Iron deposition
Primary hemochromatosis
Neonatal hemochromatosis
Secondary hemochromatosis*
Inflammation with or without myocyte necrosis*
Infective
Viral
Rickettsial
Bacterial (Lyme disease)
Protozoal (Chagas disease, toxoplasmosis)
Fungal
Parasitic
Granulomatous (sarcoid)
Giant cell myocarditis (idiopathic)
Toxic
Allergic/immunologic
Hypereosinophilic syndrome
Systemic lupus erythematosus
Dermatomyositis
Myocyte damage without inflammation*
Ischemia (coagulable and coalescent)
Toxic
Single cytolysis
Anthracycline
Cyclophosphamide
Radiation
Catecholamines
Chloroquine (Zebra bodies by EM)

Nutritional deficiencies (beriberi, selenium deficiency) Adipose tissue replacement* Obesity Steroids Parchment right ventricle and arrhythmogenic right ventricular CM

GM indicates ganglioside/mucopolysaccharide; CoA, coenzyme A; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes; MERRF, Myoclonic Epilepsy, Ragged Red Fibers; and EM, electron microscopy.

*Part of the nongenetic differential diagnosis.

Diseases that are associated with the accumulation of neutral fat frequently show changes in the ultrastructure and/or number of mitochondria. The electron microscopic findings in these disorders are not yet well characterized, and it is not clear whether specific abnormalities of mitochondrial ultrastructure are diagnostic of specific mitochondrial disorders. Biochemical assays of mitochondrial enzymes and/or molecular assays of DNA from various tissues should be used for further characterization.

The gross anatomic findings are diagnostic in two specific disorders: parchment right ventricle and isolated noncompaction of the left ventricular myocardium. In the former disorder, the right ventricular free wall is replaced with smooth muscle, fibrous tissue, and/or adipose tissue [141](#) [142](#); in the latter disorder, the left ventricular myocardium has characteristic trabeculations and deep recesses.[144](#) Asymmetrical left ventricular hypertrophy, in which the septum is disproportionately thickened, may be associated with familial hypertrophic CM, a congenital dysplasia of septal myocardial fibers. Light microscopic studies of septal transmural cross sections are necessary to confirm or rule out this diagnosis, because disarrayed myocardium cannot be sampled accurately by means of an endomyocardial biopsy. Although spatial disarray of septal myocardial fibers can be seen in control subjects and in infants with right or left ventricular pressure overload,[187](#) [188](#) [189](#) fiber disarray in >5% (and often >30%) of the total surface area of a full-thickness midseptal section is considered diagnostic of familial hypertrophic CM.[171](#) Abnormal intramyocardial coronary arteries with intimal and medial thickening have also been noted in cases of familial hypertrophic CM, often with areas of focal fibrosis or scarring.[174](#) [189](#)

Adjunctive Treatment

When a metabolic cause of CM is suspected in a child with biochemical abnormalities (hypoglycemia, metabolic acidosis, or hyperammonemia), we recommend the following treatment measures, in addition to appropriate cardiac management:

1. Careful monitoring of intake and output; levels of electrolytes, blood pH, carbon dioxide, ammonia, and glucose; neurological status; and other relevant clinical factors is critical for successful stabilization of a patient with a metabolic disorder.
2. Oral feeding should be discontinued until stabilization has occurred. The results of screening studies for disorders of amino acid and organic acid metabolism should be reviewed before oral feedings are resumed.
3. Because many of the metabolic disorders associated with CM are due to defects in the catabolic or degradative pathways of protein or fatty acid metabolism, $\geq 10\%$ dextrose solution should be given intravenously to provide energy and reduce the ongoing catabolic process and subsequent endogenous production of toxic substrate. Intravenous fluid is also necessary to treat dehydration, when present, and to promote renal clearance of toxic intermediates. Intravenous fluids should be administered carefully, especially in low-output states, to avoid rapid fluid shifts to the extravascular space. Insulin can be a useful adjunctive therapy because it stimulates anabolism, inhibits catabolism, and may lead to more efficient uptake of glucose into cells when the renal threshold for glucose is lower than normal during the initial phase of the illness. The use of solution containing lactate should be avoided because it may exacerbate any preexisting metabolic acidosis and/or lactic acidemia.
4. Correction of metabolic acidosis may help to improve brain and heart dysfunction. Intravenous sodium bicarbonate or potassium acetate solutions should be used, administered as a bolus initially, followed by an infusion. In severe metabolic crises, as much as 1 mEq of alkali per kilogram per hour may be required. However, rapid correction of the blood pH may cause a paradoxical drop in central pH and a worsening of central nervous system symptoms. The acid-base status should be monitored carefully to prevent overcorrection.
5. If metabolic acidosis is refractory to therapy or hyperammonemia is excessive, the possibility of a primary metabolic disorder must be considered. In such cases, correction of a disturbance in pH or glucose is insufficient because the toxic metabolites are not eliminated by these interventions. Until propionic acidemia and methylmalonic acidemia are ruled out, a trial of vitamin cofactors is warranted (biotin 5

mg/d PO or cyanocobalamin 1 mg/d IM, respectively). In addition, carnitine (50 to 100 mg/kg per day PO or IV) is a useful adjunct to therapy in patients with these organic acidemias or carnitine-uptake deficiency. Its use in treating disorders of long-chain fatty acid β -oxidation is anecdotal and is controversial because of a concern that long-chain acylcarnitine may be arrhythmogenic.¹⁹⁰ Dichloroacetate (2.5 to 200 mg/kg per day) acutely lowers lactic acid levels in patients with mitochondrial disorders,¹⁹¹ and trials of thiamin (20 to 3000 mg/d),¹⁹² vitamin C (250 to 2000 mg/d), and/or coenzyme Q10 (4.3 mg/kg per day) have been used empirically.

6. If the patient is comatose, is continuing to deteriorate neurologically on a metabolic basis, or has intractable acidosis or hyperammonemia, dialysis is indicated. Hemodialysis is superior to peritoneal dialysis,¹⁹³ ¹⁹⁴ and exchange transfusion is ineffective. If dialysis is not available locally, the transfer of the patient to a more specialized center should not be delayed.

Diagnostic Approach to the Moribund Patient

If a patient with CM of unknown cause presents in a moribund state and time does not permit a directed workup, it is imperative to collect certain samples and to perform studies that subsequently may establish an underlying diagnosis with implications for genetic counseling (Table 10). Premortem samples of blood (20 mL of plasma and 10 mL of whole blood) and urine (20 to 30 mL), as well as postmortem samples of fluids including vitreous humor (if urine is not available), bile, and affected tissues, should be obtained for analysis. Plasma and urine that are not analyzed immediately should be frozen at -20°C. Whole blood may be frozen directly for DNA extraction at a later time.

Table 10. Perimortem Evaluation for Suspected Genetic CM

A full autopsy or, at the very least, an autopsy limited to the heart and other major organs (skeletal muscle, liver, kidney, and brain) should be performed to obtain specimens for pathological and molecular studies. This is a delicate issue that should be discussed with the patient's family before death when possible.¹⁹⁵ Reluctant families may consent to needle biopsies, photographs, and a skeletal x-ray survey. Tissue for biochemical studies should be obtained as soon as possible after death and flash-frozen in liquid nitrogen or isopentane to minimize the loss of enzymatic activity. The results of light and electron microscopy may suggest further analyses of blood and urine that may lead in turn to appropriate enzyme or DNA studies. A skin biopsy specimen should be obtained to establish a fibroblast cell line for metabolic or enzymatic studies. These cells may also be used as a source of DNA for genetic

studies, particularly if the patient received a blood transfusion within the previous 2 days.

Future Directions

As the field of molecular genetics expands and the pathogenesis of genetic CM is better understood, the possibilities for improved diagnosis, treatment, and prevention will increase.^{6 196 197} Knowledge about the adaptive and maladaptive responses of cardiac tissue to stressed or failing myocytes (eg, hypertrophy and fibrosis, respectively) may lead to the development of new drugs that can attenuate the natural course of some forms of CM. The increasing use of cardiac transplantation raises questions about the appropriate timing with respect to the pediatric immune system and long-term efficacy. Although these medical and surgical advances have improved palliative management of heart failure, attention is now turning to the identification of underlying genetic causes. CM that is currently classified as idiopathic may in fact have a genetic basis, with the potential for diagnosis-specific treatment and cure. The application of basic science to clinical medicine has promoted the development of treatments designed to correct specific biochemical and genetic defects. In addition, the diagnosis of lethal genetic diseases for which no therapy is available currently can provide prognostic information for family planning and counseling.

Certain metabolic disorders have been treated effectively with specific dietary modifications, supplemental carnitine and vitamins, and anticipatory management during times of stress. These measures have also shown promise in the treatment and prevention of CM. Clinical and biochemical improvements and increased cardiac function have been reported with the administration of medium-chain triglycerides for long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency ¹⁹⁸ and supplemental carnitine for systemic carnitine deficiency.¹⁹⁹ Experimental measures include pantothenic acid (the precursor of coenzyme A) for the treatment of Barth syndrome ²⁰⁰ and sodium dichloroacetate for muscle cytochrome c oxidase deficiency,¹⁹¹ but clinical trials establishing their efficacy are not available currently.

Bone marrow transplantation has shown variable efficacy in the treatment of some metabolic disorders, especially storage diseases due to defects in lysosomal enzymes. Reversal of clinical and biochemical abnormalities in patients with Hurler syndrome and other mucopolysaccharidoses after bone marrow transplantation was described >10 years ago,²⁰¹ and regression of the associated CM has been reported.^{202 203 204}

Identification of specific genetic defects responsible for CM allows preclinical diagnosis through DNA-based testing in affected families and possible gene therapy. An increasing number of genetic mutations involving mitochondrial DNA have been identified in patients with CM.^{49 205 206} Many of these mutations can now be detected with the use of restriction fragment length polymorphism analysis and PCR techniques. Defects in cardiac myosin heavy-chain genes in a family with familial hypertrophic CM were detected by genetic analysis of blood lymphocytes with PCR, which resulted in identification of asymptomatic disease.²⁰⁷ As more gene defects are discovered through linkage analysis in these and other genetically heterogeneous diseases, we are beginning to correlate the clinical course and prognosis with specific mutations. Specific β -myosin heavy-chain mutations have been found to be associated with a high incidence of sudden cardiac death, whereas other mutations are associated with a better prognosis.^{133 134 149 173 208 209 210} The contribution of environmental, hormonal, and other genetic determinants requires further investigation.

One of the future treatments for CM may be direct gene manipulation, although the current results of human gene therapy clinical trials have been somewhat disappointing. Evaluation of the safety and efficacy of potential vectors is necessary for gene transfer to the terminally differentiated cells of the myocardium.²¹¹ An alternative approach to improve cardiac function may be the incorporation of healthy muscle cells into dysfunctional myocardium. Fetal cardiomyocytes or skeletal myoblasts engrafted into the hearts of mice have been induced to differentiate into adult myocardial cells forming stable, long-term, differentiated grafts.^{212 213} There is hope that this technique may prove beneficial for myocardial remodeling and repair and for the local delivery of recombinant molecules, such as growth hormone and angiogenic and neurotrophic factors, to the heart.²¹⁴

Cardiac tissue from endomyocardial biopsy samples and explanted hearts provides an opportunity to study the pathophysiology of CM at the level of the organ, cell, and gene. As the number of reported cases of pediatric CM increases, true molecular and phenotypic associations can be distinguished from coincidental occurrence. Collaboration among centers and between scientists and clinicians is essential for the most effective use of evolving information and limited technological resources, particularly since expensive laboratory tests that demand a high degree of expertise are not available at all centers. To facilitate this cooperation, a national registry for pediatric CM was established recently with an associated tissue repository to pool, track, and correlate clinical and pathological data.

Selected Abbreviations and Acronyms

ARMD = autosomal recessive muscular dystrophy

BMD = Becker-type muscular dystrophy

CM = cardiomyopathy

DMD = Duchenne muscular dystrophy

PCR = polymerase chain reaction

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