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Mitochondrial Disease: A Practical Approach for Primary Care Physicians

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ABSTRACT

Notorious variability in the presentation of mitochondrial disease in the infant and young child complicates its clinical diagnosis. Mitochondrial disease is not a single entity but, rather, a heterogeneous group of disorders characterized by impaired energy production due to genetically based oxidative phosphorylation dysfunction. Together, these disorders constitute the most common neurometabolic disease of childhood with an estimated minimal risk of developing mitochondrial disease of 1 in 5000. Diagnostic difficulty results from not only the variable and often nonspecific presentation of these disorders but also from the absence of a reliable biomarker specific for the screening or diagnosis of mitochondrial disease. A simplified and standardized approach to facilitate the clinical recognition of mitochondrial disease by primary physicians is needed. With this article we aimed to improve the clinical recognition of mitochondrial disease by primary care providers and empower the generalist to initiate appropriate baseline diagnostic testing before determining the need for specialist referral. This is particularly important in light of the international shortage of metabolism specialists to comprehensively evaluate this large and complex disease population. It is hoped that greater familiarity among primary care physicians with the protean manifestations of mitochondrial disease will facilitate the proper diagnosis and management of this growing cohort of pediatric patients who present across all specialties.

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Key Words

mitochondrial disease, oxidative phosphorylation, OXPHOS, diagnosis, children

Abbreviations

OXPHOS—oxidative phosphorylation
mtDNA—mitochondrial DNA
nDNA—nuclear DNA
MELAS—mitochondrial myopathy encephalopathy, lactic acidosis and stroke-like episodes
MRS—proton (¹H) magnetic resonance spectroscopy
CSF—cerebrospinal fluid

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THE CLINICAL RECOGNITION of mitochondrial disease is often a challenging endeavor. Genetically based, primary mitochondrial dysfunction presents as a heterogeneous group of disorders, which together are now recognized to constitute the most common neurometabolic disorder of childhood.¹ Epidemiologic studies of mitochondrial disease are limited by disease heterogeneity and underdiagnosis. Prevalence figures are less accurate than incidence figures in estimating mitochondrial disease frequency due to the high childhood mortality of these disorders. The preschool incidence was 1 in 11 000 live births in a Swedish study,² whereas the incidence of mitochondrial disease presenting by age 16 was ~1 in 16 000 live births in an Australian study.³ The Australian group combined adult prevalence figures with childhood incidence figures to arrive at an estimated minimum “birth prevalence” of 1 in 7634 live births. Allowing for incomplete ascertainment, a lifetime risk of developing mitochondrial disease of 1 in 5000 live births is a more probable estimate.^{1,4} The most common presentation of childhood-onset mitochondrial disease is Leigh syndrome, which is a progressive neurodegenerative disorder that involves developmental regression, brainstem dysfunction, and lactic acidosis, although this classic presentation only accounts for an estimated 18% of all pediatric mitochondrial disease.⁵

Mitochondrial diseases are usually progressive and multisystemic. Typically affected organs are those with a high energy demand, including skeletal and cardiac muscle, endocrine organs, kidney, nonmucosal components of the intestinal tract, retina, and the central nervous system. However, virtually any organ or tissue can be involved. As a general rule, the involvement of 3 or more organ systems without a unifying diagnosis should raise suspicion for mitochondrial disease.

Although effective treatments remain elusive, definitive diagnosis is crucial for permitting appropriate symptom management, as well as accurate prognostic and recurrence-risk counseling. Diagnostic difficulty results not only from the wide spectrum of symptoms and signs that an individual patient may have but also from the absence of a reliable screening or diagnostic biomarker that is both sensitive and specific in all cases of mitochondrial disease. Although primary mitochondrial disease by definition has a genetic etiology, the genetic abnormality may be found in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). More than 150 mtDNA pathogenic point mutations and 100 mtDNA deletions have been identified in symptomatic patients.^{6,7} However, nDNA mutations account for the majority of mitochondrial disease that presents in infants and children.^{8–10}

A simplified and standardized approach to facilitate the clinical recognition of mitochondrial disease by primary physicians is needed. With this article we aimed to assist the generalist in recognizing the most indicative

features of mitochondrial disease, standardize the definitions of primary versus secondary mitochondrial disease, and provide a consensus approach to both empower the generalist to initiate appropriate baseline diagnostic testing and aid with the decision about referral to a specialist center for what, early on, may be a nonspecific presentation.

WHEN TO SUSPECT MITOCHONDRIAL DISEASE

Red Flags

Mitochondrial disease may present with “any symptom in any organ at any age,”¹¹ but some symptoms and signs truly are more suggestive of a mitochondrial disorder than others. These “red-flag” features warrant the initiation of a baseline diagnostic evaluation for mitochondrial disease (see Table 1). In contrast, there are a multitude of nonspecific symptoms that frequently occur in infants and children with mitochondrial disease but have a broad differential diagnosis, and more often lead to other clear diagnoses (see Table 2). For example, pigmentary retinopathy in a preteenage child may certainly be a feature of primary mitochondrial disease but should also evoke the possibility of juvenile neuronal

TABLE 1 Red-Flag Findings in Mitochondrial Disease

Neurologic	Cerebral stroke-like lesions in a nonvascular pattern
	Basal ganglia disease
	Encephalopathy: recurrent or with low/moderate dosing of valproate
	Neurodegeneration
	Epilepsia partialis continua
	Myoclonus
	Ataxia
	MRI findings consistent with Leigh disease
	Characteristic MRS peaks
	Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
	Succinate peak at 2.4 ppm
Cardiovascular	Hypertrophic cardiomyopathy with rhythm disturbance
	Unexplained heart block in a child
	Cardiomyopathy with lactic acidosis (>5 mM)
	Dilated cardiomyopathy with muscle weakness
	Wolff-Parkinson-White arrhythmia
Ophthalmologic	Retinal degeneration with signs of night blindness, color-vision deficits, decreased visual acuity, or pigmentary retinopathy
	Ophthalmoplegia/paresis
	Fluctuating, dysconjugate eye movements
	Ptosis
	Sudden- or insidious-onset optic neuropathy/atrophy
Gastroenterologic	Unexplained or valproate-induced liver failure
	Severe dysmotility
	Pseudo-obstructive episodes
Other	A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
	Exercise intolerance that is not in proportion to weakness
	Hypersensitivity to general anesthesia
	Episodes of acute rhabdomyolysis

TABLE 2 Nonspecific Findings in Mitochondrial Disease

Constitutional
Failure to thrive
Short stature
Intrauterine growth retardation
Microcephaly
Neurologic
Hypotonia
Infantile spasms
Intractable epilepsy
Unexplained movement disorder
Hearing loss (sensorineural)
Axonal neuropathy
Status epilepticus with an additional red-flag or nonspecific feature
Coma
Ototoxicity to certain medications
Cardiovascular
Tachycardia (postural or paroxysmal)
Ophthalmologic
Optic nerve hypoplasia, pigmentary retinopathy
Gastroenterologic
Chronic or cyclic vomiting
Chronic unexplained constipation or diarrhea
Dermatologic
Symmetric lipomatosis
Endocrine
Hypothyroidism
Hypoparathyroidism
Idiopathic growth hormone deficiency
Renal
Renal tubular dysfunction (includes renal tubular acidosis and/or aminoaciduria)
Nephrotic syndrome
Imaging
Unexplained basal ganglia lesions
Unexplained central nervous system atrophy (cerebral or cerebellar)
Unexplained leukodystrophy
Family history
Sudden infant death syndrome
Multigenerational maternal inheritance pattern of migraine headaches, depression, or anxiety disorder

ceroid lipofuscinosis or another genetic syndrome. Thus, the nonspecific symptoms, particularly if they occur in isolation, do not indicate a mitochondrial problem per se. However, when they are present in combination, the likelihood of a mitochondrial disorder increases, partic-

ularly if the nonspecific features involve different organ systems, which should prompt initiation of appropriate baseline diagnostic investigations (see Table 3).

Lactic Acidosis

Lactate, the product of anaerobic glucose metabolism, accumulates when aerobic metabolism is impaired, which causes a shift in the oxidized-to-reduced NAD⁺/NADH ratio within mitochondria (ie, decrease in the oxidized nicotinamide-adenine dinucleotide/reduced nicotinamide-adenine dinucleotide “redox” ratio). Elevated plasma lactate and/or pyruvate levels may occur in a wide range of conditions (see Table 4). Despite their lack of specificity, an elevated plasma lactate or pyruvate level can be an important marker of mitochondrial disease. Unfortunately, the accurate interpretation of abnormal lactate and pyruvate concentrations is not always straightforward. Spurious plasma lactate elevations commonly occur as a result of physical exercise before collection, a struggling child simulating exercise of that limb, or the use of a tourniquet, which produces venous stasis during collection. Placement of an indwelling butterfly needle or catheter to permit blood-sample collection after the patient has settled for 30 minutes can resolve erroneous lactate elevations due to poor venipuncture technique. Lactate samples are usually collected into fluoride tubes (eg, as used for blood glucose measurements). As an alternative, a blood drop can be measured at bedside with a Food and Drug Administration–approved handheld lactate analyzer. Determination of pyruvate levels can also be a challenge, because they may go up or down depending on how specimens are handled. Proper handling of blood pyruvate requires that the sample be collected in 8% perchlorate, immediately placed on ice, and rapidly analyzed. It is important to pay attention to the timing of the specimen collection in relation to mealtime, because elevated pyruvate levels can occur in the first few hours after a meal in normal individuals. Therefore, elevated plasma alanine levels, when present, may be a useful indicator of long-standing pyruvate accumulation.

TABLE 3 Baseline Screening Tests for Mitochondrial Disease: Initial Evaluation

Metabolic Screening of Blood and Urine for All Patients	Metabolic Screening of Spinal Fluid for the Patient With Neurologic Symptoms	Characterize Systemic Involvement in All Patients	Clinical Neurogenetic Evaluation for the Patient With Developmental Delays
Basic chemistries	Lactate and pyruvate	Echocardiogram	Karyotype
Liver enzymes and ammonia	Quantitative amino acids	Electrocardiogram	Fragile X syndrome testing
Complete blood count	Routine studies, including cell count,	Ophthalmologic examination	Child neurology consultation
Creatinine kinase	glucose, and protein measurement	Audiology testing	Genetics consultation
Blood lactate, pyruvate, and lactate/pyruvate ratio		Brain MRI	
Quantitative plasma amino acids			
Quantitative urine organic acids			
Plasma acylcarnitine analysis			

Negative test results have a high false-negative rate. Thus, if the results are abnormal or if mitochondrial disease is still suspected, refer the patient to a mitochondrial center.

TABLE 4 Differential Diagnosis of Lactic Acidosis

Erroneous elevation
Poor collection technique (use of a tourniquet)
Poor sample handling (wrong collection tube or processing delay)
Physiological
Anaerobic exercise
Systemic diseases that increase blood lactate levels
Hypoxia
Hypotension
Shock
Sepsis
Cardiac failure/cardiomyopathy
Renal failure
Short bowel syndrome (D-lactate)
Cerebral diseases that produce increased CSF lactate levels
Prolonged seizures
Meningitis/encephalitis
Cerebral ischemia
Malignancy
Other metabolic disorders
Metabolic diseases
Amino acid disorders
Organic acidemias
Urea cycle defects
Pyruvate metabolism defects
Krebs cycle defects
Mitochondrial OXPHOS disorders
Fatty acid oxidation disorders
Disorders of liver glycogen metabolism
Disorders of liver gluconeogenesis
Biotinidase deficiency
Other
Thiamine deficiency
Toxin exposure (carbon monoxide, methanol)

Even when plasma levels of lactate and pyruvate are normal, cerebrospinal fluid (CSF) lactate levels may be elevated in patients with mitochondrial disease who have predominant brain manifestations.¹² CSF lactate levels are not influenced by collection technique, but they do rise in association with many other illnesses including seizures, stroke, intracranial infection, inflammation, and malignancy.¹³ Some patients with mitochondrial disease may have normal plasma and even normal CSF lactate levels, except during episodes of metabolic decompensation, which may be the only time an increase in lactate and/or pyruvate levels will be found. Finally, the recognition that pronounced lactate and/or pyruvate elevation is not a universal finding in mitochondrial disease demonstrates its limited utility as a diagnostic biomarker. Indeed, some disease phenotypes such as Leigh disease, Kearns-Sayre syndrome, Leber hereditary optic neuropathy, and mitochondrial polymerase γ -associated diseases frequently occur with minimal or no lactate elevation.

Neuroimaging Findings

Although results of brain imaging may be normal in a patient with pure myopathy,¹⁴ most patients with mitochondrial disease with central nervous system involve-

ment do show MRI abnormalities.^{15,16} A nonspecific, delayed myelination pattern may be seen early in the course of the disease.^{14,16,17} In addition, certain MRI findings are highly sensitive and specific for mitochondrial disease. The most common specific MRI finding is a symmetrical signal abnormality of deep gray matter, which is seen as a high signal on T2-weighted and fluid-attenuated inversion-recovery (FLAIR) MRI with a low T1-weighted signal. Any deep structure can be involved, with the character of the lesion being either patchy or homogeneous.¹⁸ Leigh disease is the prototype mitochondrial disease in which imaging findings may show involvement of the brainstem, diencephalon, basal ganglia, and cerebellum, although symmetric basal ganglia lesions are the most common finding. mtDNA-deletion disorders often involve cerebral and cerebellar atrophy with bilateral thalamic and basal ganglia lesions.^{18–20} In contrast, the imaging landmark of mitochondrial myopathy, encephalopathy lactic acidosis, and stroke-like episodes (MELAS) is infarct-like lesions that may appear only transiently and are not confined to vascular territories.^{21–23} Obtaining diffusion-weighted MRI sequences during a stroke is critical to the diagnostic workup, because lesions show an increased diffusion coefficient in mitochondrial disease but a significantly reduced diffusion coefficient in acute ischemic stroke.^{24–26}

Brain proton (¹H) magnetic resonance spectroscopy (MRS) is a newer modality that can be obtained at the time of brain MRI to noninvasively measure CSF and brain lactate levels to aid in the diagnosis and monitoring of mitochondrial disease.^{14,21,27,28} However, proton MRS abnormalities are usually only present in patients with central nervous system involvement rather than patients with “pure” myopathy. As with all diagnostic testing for possible mitochondrial disease, no single imaging test accurately defines all patients (see www.mitosoc.org and select “diagnosis toolkit” for a more extensive discussion of typical MRI and MRS findings in specific mitochondrial diseases).

The Older Child and Young Adult

Mitochondrial disease may present at any age. The symptomatic presentation of mitochondrial disease in older patients differs from that seen in infants and young children. The general rule that “the more severe the metabolic disorder, the earlier it presents in life” generally applies to mitochondrial disease. Later-onset primary (genetic) mitochondrial diseases tend to follow a chronic course, although exceptions abound. Patients may report general good health until they develop insidious signs of chronic disease or neurologic symptoms. Isolated myopathic and/or cardiomyopathy presentations, frequently with exercise intolerance, are common in teenagers and young adults. The diagnosis of fibromyalgia or chronic fatigue syndrome may be considered

before that of mitochondrial disease. In contrast, a rapidly progressive disease course may be seen with sudden regression, often in association with a physiologic stressor such as a viral illness or bacterial infection, other severe illness, pregnancy and delivery, or surgery. Regression may manifest as nonvascular stroke, ophthalmoplegia, visual decline, mental status changes, an array of new neurologic complaints, or worsening exercise tolerance and fatigue. It is important to recognize that the first episode of metabolic stroke in MELAS, or metabolic encephalopathy in Leigh disease, may be fatal at any age.

PATHOGENESIS OF MITOCHONDRIAL DISEASE

Primary Mitochondrial Disease

The term “primary mitochondrial disease” refers specifically to mitochondrial dysfunction caused by genetic mutations, directly impacting the composition and function of the electron transport chain. These defects impair mitochondrial oxidative phosphorylation (OXPHOS), the process by which oxidation of the end products of metabolism in the electron transport chain is coupled to phosphorylation of adenosine diphosphate to produce energy in the form of adenosine triphosphate. These disorders are unique in that the electron transport chain is the only metabolic pathway under dual control of both the mtDNA and nDNA genomes. Therefore, the transmission of mitochondrial disease can occur by traditional mendelian genetics or by mitochondrial genetics, the latter of which is complicated by special considerations such as heteroplasmy, threshold effect, mitotic segregation, and maternal inheritance.⁶

nDNA-Based Primary Mitochondrial Diseases

Mutations in nuclear genes are increasingly becoming recognized as the major cause of pediatric mitochondrial disease.²⁹ This occurrence is explained by the predominance of proteins expressed in the mitochondria that are synthesized by nDNA (~850 genes) compared with mtDNA (13 genes).³⁰ Autosomal recessive inheritance of nuclear genetic defects is probably the most common etiology of mitochondrial disorders in children, although mild manifestations are occasionally observed in heterozygous carriers.¹⁰

Nuclear genes implicated to date in mitochondrial disease encode proteins that are structural subunits of mitochondrial enzyme complexes, cofactors, assembly factors, translation factors, mtDNA maintenance factors, and factors that are important for the fission and fusion of this dynamic organelle. However, the specific causative gene defect has yet to be identified in most patients with probable mitochondrial disease that is suspected to be nuclear in origin. For example, the genetic basis remains a mystery in >50% of patients with complex I dysfunction, which is the largest protein complex in the

5-complex electron-transport chain and the one most commonly implicated in mitochondrial disease. The nDNA diseases that cause severe coenzyme Q₁₀ deficiency deserve special consideration as presenting a rare treatment opportunity in mitochondrial disease, because their symptoms, the onset of which may range from infancy to adulthood, usually respond to coenzyme Q₁₀ supplementation.³¹ A full discussion of the clinical findings seen in individual nDNA defects is beyond the scope of this article but has been addressed in several excellent reviews³² (see www.mitosoc.org and select “diagnosis toolkit” for a detailed discussion of the clinical presentation of nDNA-based primary mitochondrial disorders).

mtDNA-Based Primary Mitochondrial Diseases

Human mtDNA is a small 16 569-base pair molecule that encodes 37 genes. Primary mtDNA abnormalities consist of point mutations, deletions, or duplications. Point mutations are maternally inherited and may affect genes for mitochondrial transfer RNA, mRNA, ribosomal RNA, the control region, or the 13 mtDNA genes that encode electron-transport chain subunits. Deletions and duplications in mtDNA are usually sporadic. mtDNA disorders are clinically heterogeneous, but some phenotypes such as Leigh disease and MELAS are particularly common.^{6,33} Depletion of the number of copies of mtDNA in a tissue can occur, although the cause for this depletion is commonly a mutation in an nDNA gene.

Interestingly, with age, the genetic basis for mitochondrial disease is more likely to be found in mtDNA than in nDNA.^{4,34} Common primary mitochondrial diseases in older patients include mtDNA-deletion diseases (eg, chronic progressive ophthalmoplegia or Kearns-Sayre syndrome) and mtDNA point mutations in transfer RNA genes (including MELAS and Leber hereditary optic neuropathy) (see www.mitosoc.org and select “diagnosis toolkit” for a detailed discussion of the clinical presentation of primary mtDNA disorders).

Secondary Mitochondrial Disease

Even when mitochondrial dysfunction is confirmed by sophisticated biochemical testing, it can be challenging to distinguish whether the cause for this dysfunction is a gene that directly impacts the electron-transport chain (see above) or is secondary to an unrelated genetic or environmental cause. Thus, definitive diagnosis of mitochondrial disease cannot be based on biochemical findings alone, because *in vitro* electron transport chain enzyme activities in a patient’s tissue sample may be reduced secondary to other metabolic diseases or to specimen-handling issues.

Mitochondrial dysfunction, which may or may not be clinically relevant, may be seen when the primary defect occurs in another energy-related metabolic pathway, such as fatty acid oxidation³⁵ or amino acid metabolism.³⁶ In addition, OXPHOS impairment with reduction

of *in vitro* electron transport chain enzyme activity by as much as 50% has been seen in tissue samples from patients with other metabolic diseases. Indeed, other diagnoses that have ultimately been confirmed in individuals with suspected mitochondrial disease and biochemical evidence of *in vitro* mitochondrial dysfunction include copper-metabolism disorders (Wilson disease and Menkes disease^{37,38}), lysosomal disorders (neuronal ceroid-lipofuscinoses³⁹ and Fabry disease⁴⁰), peroxisomal disorders,^{41,42} pantothenate kinase-associated neurodegeneration, holocarboxylase synthetase deficiency, molybdenum cofactor deficiency, and neonatal hemochromatosis.⁴³

It is increasingly recognized that OXPHOS impairment may be contributing to the disease pathology in some genetic conditions not typically classified as mitochondrial or metabolic disorders, including Rett syndrome,⁴⁴ Aicardi-Goutières syndrome,⁴⁵ various neuromuscular disorders,⁴⁶ and Duchenne muscular dystrophy.⁴⁷ In addition, activities of electron-transport complexes in skeletal muscle may be decreased in malnourished children, with correction to normal levels after improved nutrition.⁴⁸

Medications and toxins can also significantly affect mitochondrial function. Sodium valproate may impair mitochondrial function by the induction of carnitine deficiency, depression of intramitochondrial fatty acid oxidation, and/or inhibition of OXPHOS^{49–51}; this knowledge should prompt consideration of alternative anti-convulsant use in mitochondrial disease, particularly in patients with mitochondrial polymerase γ mutations.⁵² Other important examples of drugs that may induce mitochondrial dysfunction include antiretroviral nucleoside analogues for HIV,^{53,54} as well as salicylates, which impair liver mitochondria in Reye syndrome.⁵⁵

Because many clinical features that may raise suspicion for mitochondrial diseases are nonspecific (see Table 2), the differential diagnosis can be very broad. The clinical presentation of mitochondrial disease in children can mimic other multisystem disorders such as congenital disorders of glycosylation or Marinesco-Sjögren syndrome^{56,57} or even be misinterpreted as a vascular or immunologic stroke syndrome. Although clinical and neuroimaging features of Leigh syndrome are generally strongly suggestive of a mitochondrial disorder, there are other conditions that may give rise to striatal necrosis that should be considered. Similarly, clinical and neuroimaging findings may sometimes suggest other leukoencephalopathies or neurodegenerative disorders.¹⁸

DIAGNOSTIC EVALUATION OF MITOCHONDRIAL DISEASE

The major challenge to properly establishing mitochondrial dysfunction as the cause of a patient's presentation is the absence of a definitive biomarker that characterizes mitochondrial disease in all patients. Thus, the diagnostic evaluation is necessarily multitiered and broad-

based, with a focus on integrating information from many avenues: the complete medical and family history, clinical findings that may be suggestive of mitochondrial disease (see Tables 1 and 2), biochemical laboratory abnormalities such as lactic acidosis (which, as discussed above, is neither sensitive nor specific as a single biomarker for many mitochondrial disorders), tissue-biopsy evidence of abnormal electron-transport chain enzyme activity or impaired respiratory capacity, and, if possible, the identification of a pathogenic mtDNA or nDNA mutation. This process often involves sophisticated assays that require invasive procedures such as muscle or liver biopsy to obtain tissue for testing in specialized laboratories. These investigations may give intermediate or ambiguous results, and decreased activities of electron transport chain enzymes may be secondary to nonrespiratory chain disorders.⁴³ To aid interpretation, 2 diagnostic schemes for infants and children have been proposed to categorize the likelihood of mitochondrial disease in a given patient as definite, probable, possible, or unlikely.^{58,59} Guidelines for diagnosis and treatment of mitochondrial disorders in infants and children were proposed recently by a European working group and are available in English online (<http://aps-med.de> and select "leitlinien"). However, these complex and sophisticated diagnostic algorithms are directed at the metabolic specialist and limited in their clinical utility for the generalist who is contemplating initiation of the diagnostic evaluation for a particular patient.

The diagnostic evaluation typically proceeds from general clinical evaluation to imaging and metabolic screening tests and then to more specific biochemical and genetic assays. This process starts with less invasive assays and proceeds to more invasive biopsy-based analyses as required. Clearly, the complete diagnostic process can become complicated, and enlisting the early involvement of a local metabolic specialist may be quite helpful. Referral to a metabolic specialist should always be made when symptoms and signs strongly suggest mitochondrial disease (see Tables 1 and 2), patients appear potentially unstable with classic metabolic disease features, lactic acidosis is present in blood or CSF, a maternal inheritance pattern is observed, or abnormalities are identified through baseline diagnostic evaluation (see Table 3). Referral by a primary care physician is also prudent when more elaborate testing is needed, such as provocative testing or muscle biopsy with investigation of electron-transport chain enzymes.

If a biochemical diagnosis has been made but the molecular basis remains unknown, additional genetic testing and counseling should be coordinated by a specialist. Mitochondrial disease is clearly not a single entity but, rather, a heterogeneous disorder of energy dysfunction caused by hundreds of different nuclear and mitochondrial gene mutations, and other defects. Thus, there exists no currently accepted gene-based diagnostic algo-

rithm that is useful for all patients or pursued by all metabolic specialists. Testing for nDNA mutations can be performed on any tissue, including blood. However, most diagnostic nDNA gene testing should not be performed a priori but, rather, guided by the clinical picture, tissue-specific signs, and biochemical findings in a given patient. In contrast, testing for mtDNA mutations is frequently most informative when performed on a muscle-biopsy specimen, although urinary sediment and buccal cells may also be useful specimens.⁶⁰

It is important to recognize that dietary advice should always be given in a specialized setting. In addition, although there are only a few available treatment options for mitochondrial disease, they are best offered by clinicians with experience in these disorders.

ROLE OF THE PRIMARY PRACTITIONER IN THE DIAGNOSTIC PROCESS

The relative scarcity of metabolism specialists worldwide underscores the value of having the primary physician assist, when possible, in the preliminary stages of the diagnostic evaluation by initiating appropriate baseline diagnostic testing (see Table 3). This cadre of testing is particularly useful to perform for children with “vague” presentations when the primary practitioner may be uncertain if there is sufficient evidence to warrant a metabolic referral. Similarly, normal results from baseline testing may lessen concern that a mitochondrial diagnosis is being missed. Of course, if symptoms or signs persist, worsen, or remain unexplained, consultation by a metabolic specialist may still be indicated.

CONCLUSIONS

The unique nature of the symbiotic and semiautonomous physiology of mitochondrial biology gives rise to a wide range of human mitochondrial disease. What were once regarded as a few rare diseases to be described at grand rounds or as case reports in journals are now commonly recognized disorders that are seen daily in a broad array of patient clinics. It is hoped that greater familiarity among primary care physicians with the protean but real manifestations of mitochondrial disease will facilitate the proper diagnosis and management of this growing cohort of diseases that present across all specialties.

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