Evaluation of the Child With Suspected Mitochondrial Liver Disease


Key Words: DGUOK, genetics, inborn errors of metabolism, liver disease, liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, POLG

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Mitochondrial respiratory chain defects can affect any tissue, with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). In general, clinical manifestations include multisystem involvement (liver failure, mitochondrial disease, mitochondrial hepatopathy, MPV17, mitochondrial respiratory chain defects) with the most energy-dependent organs being most vulnerable (1). The respiratory chain, consisting of 5 multimeric complexes (I–V) in the mitochondrial inner membrane, generates energy as adenosine triphosphate via electron transport and oxidative phosphorylation (Fig. 1). Defects in the respiratory chain enzymes or mitochondrial membrane transport proteins result in injury to energy-dependent organs, especially brain, retina, muscle, heart, and liver (8). In addition, hepatic mitochondria oxidize fatty acids forming ketone bodies, an important source of energy for the brain in the fasting state. Fatty acid oxidation defects, an important group of primary bioenergetic defects, can present similarly with hepatopathy or encephalopathy, often with nonketotic hypoglycemia, acidosis, and hyperammonemia, and are thus included in the differential diagnosis and should be simultaneously evaluated (9). Establishing the diagnosis of primary mitochondrial bioenergetic defects in patients with liver disease requires a high index of suspicion in specific clinical scenarios. A tiered diagnostic evaluation is useful (Table 1). Although mitochondrial hepatopathies are a heterogeneous group of disorders, there are several general laboratory investigations in blood and urine that can reveal an altered redox status suggestive of respiratory chain defects (lactate/pyruvate molar ratios and ketone body ratios). Specific laboratory tests are considered in patients with unique clinical presentations as well, and either tissue analysis or genotyping is used to identify the etiology. Other typically involved organ systems should be evaluated when mitochondrial hepatopathy is suspected (Table 2). Several important management issues should be addressed during this evaluation process. These guidelines outline the evaluation of the infant or child with suspected mitochondrial hepatopathy. Two summary tables (Tables 3 and 4) describing each genetic etiology follow. Reference clinical laboratories for the genetic tests can be found at www.genetests.org.

Clinical Scenarios Suggesting Possible Mitochondrial Liver Disease

Mitochondrial liver disease can present acutely in a child with no history of hepatic dysfunction, or with chronic liver and...
mutations is urgent in infants with acute BCS1L = MPV17 < The respiratory chain, consisting of 5 multimeric complexes (I–V) in the mitochondrial inner membrane, generates energy as adenosine triphosphate (ATP) via electron transport and oxidative phosphorylation.

Tissue evaluation

Genotyping for more common genes

Most common with liver involvement: POLG1 (12,13), DGUOK (14–16), MPV17 (17,18), SUCLA1 (19), C10ORF2/TWINKLE (20), TRMU (28,29) (see Tables 3 and 4)

If neuromuscular features suggest MELAS or pancreatic insufficiency suggests Pearson marrow/pancreas syndrome: mitochondrial DNA point mutations/deletions (21)

If methylmalonic acid is elevated: SUCLA1 (19)

If acylcarnitines and/or urine organic acids suggest specific FAO defects: genotyping for LCHAD (22), CPTI and II deficiency (23,24), or (MADD = glutaric acidemia II = ETF and ETF-DH deficiency) (25), SLC25A20 for CACT deficiency (26)

For recurrent acute liver failure: TRMU, ACDAP, CPTI, SUCLA1 (19,23,27,28). Identification of TRMU mutations is urgent in infants with acute liver failure because these patients frequently recover without the need for transplantation (28,29)

Note: Next-generation sequencing (eg, exome sequencing) will allow for simultaneous evaluation of panels of all nuclear genes encoding mitochondrial proteins and all mitochondrial DNA genes at considerably lower cost in the future, encompassing the above gene tests, and will eventually replace single gene sequencing. It is already available in some countries

TABLE 1. Tiered approach to evaluation of suspected mitochondrial disease

<table>
<thead>
<tr>
<th>Tier</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Early screening</td>
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<tr>
<td></td>
<td>Comprehensive metabolic profile, INR, α-fetoprotein, CPK, phosphorus, complete blood cell count, and ammonia</td>
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<td>Lactate/pyruvate, ideally obtained 1 hour after feeding (normal molar ratio is &lt;0.2, normal postprandial lactate &lt;2.8 mmol/L)</td>
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<td></td>
<td>Serum ketone bodies: both quantitative 3-hydroxybutyrate and quantitative acetocetate (3-hydroxybutyrate/acetocetate ratio &lt;4 is normal) and total free fatty acids to calculate ketone bodies: free fatty acid ratio (10)</td>
</tr>
<tr>
<td></td>
<td>Serum acylcarnitine profile; serum-free and total carnitines</td>
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<tr>
<td></td>
<td>Urine organic acids (look for elevated lactate, succinate, fumarate, malate, 3-methylglutaconic or 2-hydroxyglutaric, 2-ketoglutaric, methylmalonic acid)</td>
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<td></td>
<td>Serum amino acids (look for elevation of alanine [abnormal &gt;500 µmol/L, but more specific if &gt;600 µmol/L])</td>
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<td></td>
<td>Consider: Quantitative 3-methylglutaconic acid (serum or urine) (11)</td>
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<td></td>
<td>Urine acylglycines and 2-ethylmalonic quantification (if multiple acyl-CoA dehydrogenase deficiency is suspected)</td>
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<td></td>
<td>Thymidine (plasma) (especially in cases with coexistent intestinal dysmotility concerning for MNGIE syndrome)</td>
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<td>Coenzyme-Q levels in leukocytes, not serum (for CoQ deficiency; leukocyte levels correlate better with tissue CoQ levels, whereas serum levels reflect nutritional status)</td>
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<td></td>
<td>Quantitative serum methylmalonic acid (elevated in SUCLA and SUCLG1 deficiencies)</td>
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<td></td>
<td>CSF analysis: lactate and pyruvate (if blood lactate is normal but evidence of CNS involvement), amino acids (especially elevated CSF alanine), and protein concentration (note CSF protein can be elevated in POLG1 disease early on, even when lactate is normal)</td>
</tr>
<tr>
<td>2</td>
<td>Genotyping for more common genes</td>
</tr>
<tr>
<td></td>
<td>Most common with liver involvement: POLG1 (12,13), DGUOK (14–16), MPV17 (17,18), SUCLA1 (19), C10ORF2/TWINKLE (20), TRMU (28,29) (see Tables 3 and 4)</td>
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<td>If neuromuscular features suggest MELAS or pancreatic insufficiency suggests Pearson marrow/pancreas syndrome: mitochondrial DNA point mutations/deletions (21)</td>
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</tr>
<tr>
<td>3</td>
<td>Tissue evaluation</td>
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<tr>
<td></td>
<td>Liver biopsy:</td>
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<td>Light microscopy, electron microscopy (place specimen in glutaraldehyde); consider oil red O stain for fat on frozen section; consider iron stain if DGUOK or BCS1L are suspected (Fig. 2)</td>
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<td>Frozen tissue for respiratory chain enzyme activity analysis</td>
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<td></td>
<td>Consider storing frozen tissue for future studies if amount adequate. Consider blue native PAGE gel analysis with in-gel activity staining (Fig. 3)</td>
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<td></td>
<td>Skin biopsy for fibroblast culture. Can be used for FAO enzyme activity, respiratory chain enzyme activities, blue native PAGE testing (30). FAO probe studies (especially if acylcarnitine profile is abnormal), or high-resolution respirometry (31). Note: Because of heteroplasmy of mitochondrial genes or because of differential tissue expression of nuclear genes, abnormalities in patients with mitochondrial hepatopathy can sometimes only be confirmed in liver tissue</td>
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<tr>
<td></td>
<td>Muscle biopsy, especially if muscle involvement is present: light and electron microscopy. Consider histochemistry for respiratory chain complexes, respiratory chain enzyme assays, blue native PAGE analysis, mtDNA depletion analysis, mtDNA whole genome sequencing, and/or deletion analysis</td>
</tr>
</tbody>
</table>

(Continued)
Further molecular and biochemical evaluation

Additional genes to consider: TRMU (28), BCS1L (32), SCO1 (33), TSFM (34), TWINKLE (5,20), ACAD9 (27) (the latter especially if episodes of liver failure and fatty acid oxidation defect) (see Tables 3 and 4). Not all of these tests may be clinically available. A microarray is available to evaluate for large deletions or duplications in nuclear or mitochondrial genes (35). Note: Next-generation sequencing (eg, exome sequencing) will allow for simultaneous evaluation of panels of all genes encoding mitochondrial proteins and many or all mitochondrial DNA genes at considerably lower cost in the future, and will eventually replace single gene sequencing. At present, its efficacy is highest in clinically and biochemically well-characterized patients.

Targeted molecular analyses based on the results of tissue-based respiratory chain enzyme assays and primary liver disease as presentation:

- Isolated complex I deficiency: ACAD9 (27)
- Isolated complex III deficiency: BCS1L (32)
- Isolated complex IV deficiency: SCO1 (33)

Combined complex I, III, and IV deficiency with incompletely assembled complex V bands on blue native PAGE (this signifies a generic defect in the processing of mtDNA encoded subunits (36)). It can be caused by a deficiency of mtDNA (mtDNA depletion syndromes) or by a defect in transcription or translation.

If mtDNA content is <5% of normal in liver: mtDNA depletion syndrome: POLG1, POLG2, TWINKLE, DGUOK, and TYMP (37)

With normal or mildly decreased mtDNA but with multiple deletions (assay with long-range PCR or with next-generation mtDNA analysis): same as above, but more often with POLG or TWINKLE or TYMP

With normal or (more common) elevated mtDNA: translation defects such as EF-Tu, EGF-1, TSFM, TRMU, FARS2 (and other tRNA synthase genes, tRNA modification genes, ribosomal genes, translation initiation, elongation and termination factors) (28,34,38).

Consider exome or mito-exome sequencing for the many genes associated with the translational machinery.

Deficiency of combined complex II–III assay but normal isolated assay II and normal III indicates a likely CoQ deficiency. Obtain CoQ levels, and review for causes of CoQ deficiency (39).

**TABLE 1. (Continued)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIERED DIAGNOSTIC EVALUATION</strong></td>
<td>A wide array of tests that are useful in establishing the diagnosis of mitochondrial hepatopathies is available. These tests range from simple, inexpensive, easily available screening tests to extremely expensive, widely ranging genetic studies. In the child who is suspected of having a mitochondrial disease, a tiered approach to diagnostic testing is recommended. Early screening tests (tier 1) may provide clues to abnormalities in energy metabolism, and results of these tests may guide subsequent confirmatory testing to establish a molecular diagnosis. Genotyping is available clinically for the more common mitochondrial diseases (tier 2); the clinical scenario or results of screening tests can inform the choice of genetic tests. For example, a panel screening for specific gene mutations in DGUOK, POLG1, and MPV17 responsible for infantile liver failure with lactic acidosis and mitochondrial DNA depletion is readily available and may be useful early in evaluation (see Table 3). The diagnostic role of next-generation sequencing (NGS), which is now allowing sequencing of &gt;100 genes involved in mitochondrial diseases with a single blood test and at relatively low cost (42), or even whole exome or genome sequencing, will become increasingly important and will eventually replace genotyping single genes or small panels of genes in tier 2; however, the identification of multiple gene variants of uncertain significance will require detailed clinical and biochemical confirmation for interpretation. Tissue may also be needed to make a specific biochemical diagnosis, particularly if the liver is the major or sole affected organ (tier 3; Fig. 2). Occasionally, diagnostic findings will only be revealed in liver tissue rather than in blood, muscle, or skin fibroblasts. When further clarification is needed, genotyping for less common disease-causing genes may be required (tier 4); however, the use of NGS earlier on in the evaluation process in the future (in tier 2) may obviate the need for this step in the evaluation paradigm. At present, the diagnostic yield of NGS of all mitochondrial genes is high in patients with well-characterized mitochondrial disease, in particular with biochemical evidence of mitochondrial enzymatic dysfunction (42), but is low in patients with only a clinical suspicion (43). Biochemical studies evaluating the structure and function of mitochondrial subunits in the affected tissue can be performed as needed.</td>
</tr>
</tbody>
</table>

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Central nervous system (CNS) disease. Fulminant or acute liver failure is 1 important presentation of mitochondrial disease (41). Especially in a young child or in one with preexisting or disproportionate CNS involvement, mitochondrial disease is in the differential diagnosis of acute liver failure. More important, if liver transplant is being considered, careful attention must be paid to potential extrahepatic manifestations of mitochondrial dysfunction. Another clinical presentation is chronic liver disease, manifested by elevated aminotransferases, hepatomegaly, cholestasis, cirrhosis, and especially steatohepatitis; these may be accompanied by other indicators of mitochondrial disease, including hypoglycemia or lactic acidosis. Third, liver disease accompanied by chronic neuromuscular disease or disease in other organ systems may be a sign of mitochondrial disease.

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**TABLE 2. Evaluation for disease in other organ systems**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Neurologic examination, MR/MR spectroscopy, EEG, CSF</td>
</tr>
<tr>
<td>Heart</td>
<td>EKG</td>
</tr>
<tr>
<td>Muscle</td>
<td>Muscle biopsy</td>
</tr>
<tr>
<td>Eyes</td>
<td>Detailed ophthalmologic examination</td>
</tr>
<tr>
<td>Kidney</td>
<td>Electrolytes, serum and urine phosphorus and creatinine, urine amino acids, urinalysis, urine protein</td>
</tr>
<tr>
<td>Endocrine</td>
<td>HbA1c, morning cortisol</td>
</tr>
<tr>
<td>Pancreas (exocrine)</td>
<td>Fecal pancreatic elastase, endoscopic pancreatic stimulation test</td>
</tr>
<tr>
<td>Hearing</td>
<td>Hearing testing</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; EEG = electroencephalogram; EKG = electrocardiogram; HbA1c = hemoglobin A1c; MR = magnetic resonance.
<table>
<thead>
<tr>
<th>Mutation/syndrome</th>
<th>Defect</th>
<th>Onset/age at presentation</th>
<th>Hepatic presentation</th>
<th>Neurological features</th>
<th>Other features</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DGUOK (14–16)</strong></td>
<td>mtDNA depletion complex I, III, IV</td>
<td>Acute/early neonatal</td>
<td>Neonatal liver failure, progressive, cholestasis, neonatal hemochromatosis, hepatocellular carcinoma risk, can have isolated liver disease</td>
<td>Hypotonia, developmental regression, nystagmus</td>
<td>Lactic acidosis, hypoglycemia</td>
<td>DGUOK sequence analysis</td>
</tr>
<tr>
<td><strong>POLG (12,13)</strong></td>
<td>mtDNA depletion complex I, III, IV</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, micro- or macrovesicular steatosis, cirrhosis</td>
<td>Encephalopathy, seizures, myopathy, neuropathy, blindness, developmental regression</td>
<td>Vomiting, GERD</td>
<td>POLG sequence analysis or panel</td>
</tr>
<tr>
<td><strong>MPV17/Navajo neurohepatopathy (17,18)</strong></td>
<td>mtDNA depletion complex I, III, IV</td>
<td>Acute/neonatal</td>
<td>Isolated neonatal/infant liver failure or in multisystem syndrome</td>
<td>Sensorimotor neuropathy, progressive CNS white matter lesions</td>
<td>Acidosis, FTT, corneal anesthesia/abrasions, acral mutilation</td>
<td>MPV17 sequence analysis or panel</td>
</tr>
<tr>
<td><strong>TWINKLE (PEO1) (C100RF2) (5,20)</strong></td>
<td>mtDNA depletion</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, cirrhosis, elevated liver enzymes</td>
<td>Encephalopathy (athetosis, ataxia, seizures), sensory neuropathy, deafness</td>
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<tr>
<td><strong>TRMU (28,29)</strong></td>
<td>Decreased mitotranslation (tRNA-modifying enzyme) complex I, III, IV</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, some recover, possibly with cirrhosis</td>
<td></td>
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<tr>
<td><strong>TSFM, EFG1, EF-Tu, MRPS16 (34)</strong></td>
<td>Decreased mitotranslation (elongation)</td>
<td>Acute/neonatal</td>
<td>Liver dysfunction in infancy, hepatomegaly</td>
<td>Hypotonia, dystonia</td>
<td>Hypertrophic cardiomypathy, tubulopathy</td>
<td>Sequencing individual genes, e.g., TSFM or exome sequencing</td>
</tr>
<tr>
<td><strong>SUCLG1 (19)</strong></td>
<td>mtDNA depletion abnormal succinate synthesis complex I, III, IV</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, episodic liver failure</td>
<td>Hypotonia/myopathy (progressive), hearing loss</td>
<td>Acidosis, elevated methylmalonic acid</td>
<td>SUCLG1 sequence analysis</td>
</tr>
<tr>
<td><strong>BCSIL (32)</strong></td>
<td>Complex III assembly deficiency</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, cholestasis, hepatic iron overload</td>
<td>Growth failure, aminoaciduria, lactic acidosis, early death (GRACILE syndrome)</td>
<td></td>
<td>BCSIL sequence analysis</td>
</tr>
<tr>
<td><strong>SCO1 (33)</strong></td>
<td>Complex IV deficiency</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, hepatomegaly</td>
<td>Hypotonia</td>
<td>Acidosis</td>
<td>SCO1 sequence analysis</td>
</tr>
<tr>
<td><strong>FARS2 (58)</strong></td>
<td>Phenylalanine tRNA synthetase</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure (Alper-like)</td>
<td>Intractable seizures, encephalopathy</td>
<td></td>
<td>FARS2 sequence analysis on Nexgen</td>
</tr>
<tr>
<td><strong>SLC25A20 (26)</strong></td>
<td>Carnitine acylcarnitine translocase deficiency (carnitine, FAO)</td>
<td>Acute/neonatal</td>
<td>Neonatal liver failure, steatohepatitis</td>
<td>Myopathy</td>
<td>Hypoglycemia, cardiomypathy</td>
<td>SLC25A20 sequence analysis</td>
</tr>
<tr>
<td><strong>HADHA/LCHAD or trifunctional protein deficiency (22)</strong></td>
<td>FAO defect</td>
<td>Acute</td>
<td>Hepatomegaly, fatty liver, elevated LFTs, cholestasis, liver failure, ALF</td>
<td>Encephalopathy, peripheral neuropathy</td>
<td>Acidosis, hypoglycemia, pigmentary retinopathy</td>
<td>HADHA sequence analysis</td>
</tr>
<tr>
<td><strong>CPT I deficiency (23)</strong></td>
<td>Carnitine cycle FAO defect</td>
<td>Acute/infancy</td>
<td>Hepatomegaly, liver failure episodes</td>
<td>Reye-like episodes of encephalopathy</td>
<td>Hypoketotic hypoglycemia</td>
<td>CPTIA sequence analysis</td>
</tr>
<tr>
<td><strong>CPT II deficiency (23,24)</strong></td>
<td>Carnitine cycle FAO defect</td>
<td>Acute/severe neonatal</td>
<td>Liver failure in infancy</td>
<td>Seizures</td>
<td>Hypoketotic hypoglycemia, cardiomypathy, myopathy</td>
<td>CPT2 sequence analysis</td>
</tr>
</tbody>
</table>

ALF = acute liver failure; CNS = central nervous system; CoA = coenzyme A; CPT = carnitine palmitoyltransferase; FAO = fatty acid oxidation; FTT = failure to thrive; GERD = gastroesophageal reflux disease; HADHA = hydroxyacyl-CoA deHase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase alpha subunit; LCHAD = long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LFTs = liver function tests.
<table>
<thead>
<tr>
<th>Mutation/syndrome</th>
<th>Defect</th>
<th>Onset/age at presentation</th>
<th>Hepatic presentation</th>
<th>Neurological features</th>
<th>Other features</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGUOK (15)</td>
<td>mtDNA depletion complex I, III, IV</td>
<td>Late presentation</td>
<td>Progressive cholestasis, may have iron overload, HCC risk</td>
<td>Hypotonia, developmental regression, nystagmus</td>
<td>Lactic acidosis</td>
<td>DGUOK sequence analysis</td>
</tr>
<tr>
<td>MPV17/Navajo neurohepatopathy (18)</td>
<td>mtDNA depletion complex I, III, IV</td>
<td>Chronic/neonatal to childhood</td>
<td>Progressive liver disease or in multisystem syndrome</td>
<td>Sensorimotor neuropathy, progressive CNS white matter lesions</td>
<td>Acidosis, FTT, corneal anesthesia, abrasion, acral mutilation</td>
<td>MPV17 sequence analysis</td>
</tr>
<tr>
<td>POLG/Aper disease (12,13)</td>
<td>mtDNA depletion complex I, III, IV deficiency</td>
<td>Subacute: toddlers, young adults</td>
<td>Later-onset liver failure, macro- or microvesicular steatosis, cirrhosis</td>
<td>Intractable seizures and developmental regression, blindness, neuropathy, ataxia</td>
<td>Vomiting, GERD</td>
<td>POLG sequence analysis</td>
</tr>
<tr>
<td>TWINKLE (C10orf2) (20)</td>
<td>mtDNA depletion DNA helicase</td>
<td>Chronic</td>
<td>Neonatal liver failure, cirrhosis, elevated liver enzymes</td>
<td>Encephalopathy (athetosis, ataxia, seizures), sensory neuropathy, deafness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUCLG (19)</td>
<td>mtDNA depletion, abnormal succinate synthetase (ATP generation)</td>
<td>Chronic or episodic</td>
<td>Episodes of liver failure</td>
<td>Hypotonia/myopathy (progressive), hearing loss</td>
<td>Acidosis</td>
<td>SUCCLG1 sequence analysis</td>
</tr>
<tr>
<td>ACAD9 (27)</td>
<td>FAO defect, complex I assembly</td>
<td>Episodic</td>
<td>Episode of liver failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYMP/MNGIES (37)</td>
<td>Thyamine phosphorylase deficiency, complex IV</td>
<td>Chronic</td>
<td>Liver dysfunction, macrovesicular steatosis, cirrhosis</td>
<td>Leukoencephalopathy, ophthalmoplegia, ptosis, peripheral neuropathy, hearing loss</td>
<td>Pseudo-obstruction, GERD</td>
<td>ACAD9 sequencing and deletion analysis, Plasma thymidine and deoxyuridine levels, TP enzyme activity, TYMP sequencing</td>
</tr>
<tr>
<td>Villous atrophy syndrome (40)</td>
<td>Complex III defect</td>
<td>Chronic/early childhood</td>
<td>Hepatomegaly, raised liver enzymes, steatosis</td>
<td>Cerebellar ataxia, sensorimotor deafness, seizures</td>
<td>Vomiting, anorexia, chronic diarrhea (resolved later in life), villous atrophy, lactic acidosis, DM</td>
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<tr>
<td>Pearson syndrome (21)</td>
<td>mtDNA deletion complex I, III, VI</td>
<td>Chronic/infancy</td>
<td>Cirrhosis with hepatomegaly, cholestasis, raised liver enzymes, progressive liver failure, death in early childhood</td>
<td></td>
<td>Refractory sideroblastic anemia, vacuolization of marrow precursors, variable neutropenia and thrombocytopenia, lactic acidosis, pancreatic insufficiency</td>
<td>mtDNA common mutations and deletions screening</td>
</tr>
<tr>
<td>HADHA/LCHAD or trifunctional protein deficiency (22)</td>
<td>FAO defect</td>
<td>Chronic, infancy or later</td>
<td>Hepatomegaly, fatty liver, elevated LFTs, cholestasis, liver failure, acute fatty liver of pregnancy</td>
<td>Encephalopathy, peripheral neuropathy</td>
<td>Acidosis, hypoglycemia, pigmentary retinopathy</td>
<td>HADHA sequence analysis</td>
</tr>
<tr>
<td>CPT2/CPT2 deficiency (24)</td>
<td>Carnitine cycle FAO defect</td>
<td>Infants with liver failure</td>
<td>Liver failure episodes</td>
<td>Seizures</td>
<td>Hypoketotic hypoglycemia, cardiomyopathy, myopathy, rhabdomyolysis</td>
<td>CPT2 sequence analysis</td>
</tr>
<tr>
<td>MADD (glutaric acidemia II) (25)</td>
<td>FAO defect complex II, III</td>
<td>Chronic, infancy up to adulthood</td>
<td>Hepatomegaly, steatosis</td>
<td>Neurologic symptoms, myopathy</td>
<td>Hypoglycemia, acidosis</td>
<td>Sequence of ETF A, B, or ETF-DH</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; CNS = central nervous system; CoA = coenzyme A; CPT = carnitine palmitoyltransferase; DM = diabetes mellitus; FAO = fatty acid oxidation; FTT = failure to thrive; GERD = gastroesophageal reflux disease; HADHA = hydroxyacyl-CoA dehydrogenase 3-ketoacyl-CoA thiolase/acyl-CoA dehydrogenase alpha subunit; HCC = hepatocellular carcinoma; LCHAD = long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LFTs = liver function tests; MADD = multiple acyl-CoA dehydrogenase deficiency; MNGIES = mitochondrial neurogastrointestinal encephalopathy syndrome.
specifically to determine whether new genetic variants have a functional effect (Fig. 3). Thus, a combination of biochemical and molecular studies may be needed to confirm the pathologic nature of new gene variants to be described in the future. Table 1 outlines a tiered approach to diagnostic evaluation.

Tables 3 and 4 catalog known mitochondrial hepatopathies and briefly describe the mutation, defect, clinical description, and diagnostic testing. The typical hepatic presentation, ranging from hepatic failure to cholestasis to steatohepatitis to cirrhosis, is briefly outlined; neurologic symptoms and other systems involved are briefly reviewed and references are provided. The disorders are separated into those with a neonatal or an infantile presentation (Table 3) and those with later or more chronic onset (Table 4). There is, however, overlap between these 2, and new diseases and presentations are recognized frequently.

EVALUATION FOR DISEASE IN OTHER ORGAN SYSTEMS

As part of the evaluation for mitochondrial hepatopathies, a systematic approach also needs to be instituted to search for involvement of other affected organ systems (Table 2). This takes on particular significance when liver failure occurs in a child with suspected mitochondrial disease because the decision to consider liver transplantation is especially challenging. Because mitochondrial disease usually involves multiple organ systems and is generally progressive in other organs even following liver transplantation, there are many uncertainties regarding liver transplantation. Possible posttransplant appearance of new progressive symptoms in organs uninvolved before liver transplantation also needs to be considered (44–47). Establishing criteria for liver transplantation in mitochondrial hepatopathies is beyond the scope of this article; however, in the evaluation for transplantation,
meticulous evaluation for disease in other organ systems is para-
mount, especially because results of testing for specific disorders
can be delayed by weeks. Evaluation of the CNS is critical. Besides
a careful neurologic examination, magnetic resonance imaging of
the brain is done to evaluate for Leigh disease, cerebellar atrophy,
leukodystrophy, and cerebral atrophy. Magnetic resonance spec-
troscopy can be especially helpful, but blood lactate >3 mmol/L
may affect interpretation. Evaluation can also include electroence-
phalography and cerebrospinal fluid examination (see above). To
evaluate for cardiomypathy, electrocardiogram and echocardio-
gram should be done. A detailed ophthalmologic examination
may reveal ophthalmoplegia in DGUOK deficiency, retinopathy
in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency or
respiratory chain defects, cornel abrasions in MPV17, or optic
atrophy in POLG disease. Serum electrolytes, serum and urine
phosphorus and creatinine, urine amino acids, urinalysis, and urine
protein are measured to evaluate renal function because abnormal
tubular function may suggest a defect in BCSIL. Because diabetes
mellitus and even adrenal insufficiency can be seen in mitochon-
drial disorders, HbA1c and morning cortisol level should be con-
sidered. Pancreatic insufficiency is seen in some mitochondrial
diseases and may be detected by measuring fecal pancreatic elas-
tase. Hearing screening should be performed.

MANAGEMENT DURING EVALUATION FOR
POSSIBLE MITOCHONDRIAL DISEASE

The child with mitochondrial disease can be vulnerable to
metabolic perturbations such as hypoglycemia or acidosis; close
monitoring is important. It is important to discontinue or avoid
medications that may exacerbate hepatopathy or impair mitochon-
drial function or mtDNA translation or transcription, including
sodium valproate, tetracycline, and macrolide antibiotics, reverse
transcriptase inhibitors (particularly azathiprione), chlorampheni-
col, quinolones, and linezolid (48). Use of Ringer lactate intrave-
nous solution should be avoided because the liver may not be able to
metabolize lactate; propofol should be avoided during anesthesia or
sedated procedures because the drug can interfere with mitochon-
drial function (49). The goal is to maintain anabolism using a
balanced intake of fat and carbohydrates with at least 75% of
normal energy intake while avoiding unbalanced intakes (eg,
glucose only at high intravenous rate) or fasting for >12 hours
(50). In patients with preexisting lactic acidosis, lactate levels
should be monitored around procedures to avoid excessive lactic
acidosis.

CONCLUSIONS

Mitochondrial disease can present from infancy to adulthood
with varying degrees of hepatic and extrahepatic involvement. In
the last decade, there has been a rapid expansion of newly recog-
nized mitochondrial diseases and their molecular bases. Available
technology to aid in diagnosis has improved substantially. None-
theless, diagnosis of suspected mitochondrial disease in children is
complicated; a systematic clinical, biochemical, and molecular
approach can aid in making a timely, accurate, and cost-effective
diagnosis.

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