Published in final edited form as:

Semin Liver Dis. 2007 August ; 27(3): 259–273. doi:10.1055/s-2007-985071.

Liver Disease in Mitochondrial Disorders

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Abstract

Liver involvement, a common feature in childhood mitochondrial hepatopathies, particularly in the neonatal period, may manifest as neonatal acute liver failure, hepatic steatohepatitis, cholestasis, or cirrhosis with chronic liver failure of insidious onset. There are usually significant neuromuscular symptoms, multisystem involvement, and lactic acidemia. The liver disease is usually progressive and eventually fatal. Current medical therapy of mitochondrial hepatopathies is largely ineffective, and the prognosis is usually poor. The role of liver transplantation in patients with liver failure remains poorly defined because of the systemic nature of the disease that does not respond to transplantation. Several specific molecular defects (mutations in nuclear genes such as *SCO1*, *BCS1L*, *POLG*, *DGUOK*, and *MPV17* and deletion or rearrangement of mitochondrial DNA) have been identified in recent years. Prospective, longitudinal multicenter studies will be needed to address the gaps in our knowledge in these rare liver diseases.

Keywords

Mitochondrial hepatopathies; genetics; pathogenesis

Mitochondria are double-membrane intracellular organelles containing a soluble matrix and their own unique genome.¹ They are the main source of the high-energy phosphate molecule adenosine triphosphate (ATP), which is essential for all active intracellular processes.¹ Structural and functional alterations of mitochondria are increasingly being recognized in the pathogenesis of a group of diseases, including involvement of the central and peripheral nervous systems, skeletal muscle, bone marrow, the endocrine and exocrine pancreas, kidney, myocardium, and intestines.^{1–3} Because the metabolically active liver requires continuous synthesis of ATP, hepatocytes contain a relatively high density of mitochondria compared with other cells. Disorders affecting mitochondrial oxidative phosphorylation (OXPHOS) and hepatocellular metabolism directly influence fatty acid oxidation, resulting in impaired bile flow and steatosis, cell death, and fibrogenesis.^{1,4–6} Mitochondrial hepatopathies present clinically primarily in early childhood; however, secondary disorders present at any age. Significant recent advances have occurred in our understanding of mitochondrial hepatopathies, including identification of the molecular basis of many disorders. This review will describe recent development in primary mitochondrial hepatopathies, including the genetics, management, and the future directions for research.

MITOCHONDRIAL STRUCTURE, FUNCTION, AND GENETICS

ATP is produced by the respiratory chain on the inner mitochondrial membrane by OXPHOS (Fig. 1).¹ In this process, reduced cofactors (reduced nicotinamide adenine dinucleotide [NADH], reduced flavin adenine dinucleotide [FADH₂], and electron transfer flavoprotein [ETF]) generated from the intermediary metabolism of carbohydrates, proteins, and lipids donate electrons to complexes I and II and ubiquinone, which then flow down an electrochemical gradient to complexes III, cytochrome *c*, and finally to complex IV, resulting in the active translocation of protons (H⁺) out of the mitochondrial matrix into the intermembrane space, which establishes an electrochemical gradient. At complex V, protons flow back into the mitochondrial matrix, and the released energy is used to synthesize ATP.^{1,2}

A unique feature of mitochondria in mammalian cells is the presence of a distinct genome, mitochondrial DNA (mtDNA), which is independent from that of the nucleus.⁴ A typical hepatocyte contains ~1000 copies of mtDNA. Both nuclear and mtDNA genes encode for respiratory chain peptide components. Thirteen essential polypeptides are synthesized from the small 16.5-kb, circular double-stranded mtDNA. In contrast, nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA.^{1,3} These genes include DNA polymerase- γ (*POLG*), thymidine kinase 2 (*TK2*), and deoxyguanosine kinase (*DGUOK*).³ mtDNA also encodes the 24 transfer RNAs (t-RNAs) required for intramitochondrial protein synthesis.¹

An important feature of mitochondria is that virtually all mtDNA is derived from the unfertilized oocyte.⁴ Most researchers believe that virtually no paternal mtDNA from the sperm survives entry into the fertilized ovum at the point of conception, the embryo thus developing with maternal mtDNA alone. Possible explanations for this phenomenon include suppression of paternal mtDNA, or dilution beyond the limits of detection and to levels at which its contribution would in any case be irrelevant.^{7,8} This maternal inheritance in mtDNA disorders is important for genetic counseling.

EPIDEMIOLOGY OF PRIMARY MITOCHONDRIAL HEPATOPATHIES

Recent studies have shown that mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children under 16 years of age.⁹ In a population-based study of the prevalence of mitochondrial encephalomyopathies in Sweden, liver involvement was noted in 20% of the cases studied.¹⁰ In another study of 1041 children from a tertiary referral center, 22 (10%) of the 234 patients with respiratory chain defects had liver dysfunction, and 10 patients had the onset of liver disease in the neonatal period.¹¹ Given the heterogeneity of the features and difficulties with establishing these diagnoses, these figures are likely to be underestimates of the true prevalence of these disorders.

CLASSIFICATION OF MITOCHONDRIAL HEPATOPATHIES

A striking feature of mitochondrial disorders is their clinical heterogeneity, ranging from single-organ involvement to severe multi-system disease.^{11–13} Hepatic manifestations of mitochondrial disorders range from hepatic steatosis, cholestasis, and chronic liver disease with insidious onset to neonatal liver failure, frequently associated with neuromuscular symptoms.² Sokol and Treem² have proposed a classification scheme for mitochondrial hepatopathies (Table 1), which includes *primary disorders*, in which the mitochondrial defect is the primary cause of the liver disorder, and *secondary disorders*, in which a secondary insult to mitochondria is caused by either a genetic defect that affects nonmitochondrial proteins or by an acquired (exogenous) injury to mitochondria.⁴ Leonard and Shapiro¹⁴ have further divided primary mitochondrial diseases into those caused by

mutations affecting mtDNA genes (class 1a) and those caused by mutations in nuclear genes that encode mitochondrial respiratory chain proteins or cofactors (class 1b).

CLINICAL FEATURES OF PRIMARY MITOCHONDRIAL HEPATOPATHIES

The clinical presentation of mitochondrial hepatopathies is heterogeneous, including neonatal acute liver failure, lactic acidosis, cholestasis, or chronic liver failure (Tables 2 and 3).

Neonatal Liver Failure

Mitochondrial hepatopathies involving respiratory chain defects frequently present as acute liver failure with onset within the first weeks to months of life. Associated features include lethargy, hypotonia, vomiting, poor suck, and seizures.^{11,12} In others, after an initial normal course, a viral infection or some other undefined inciting event triggers hepatic and, sometimes, neurologic deterioration.¹¹ Most infants also have severe neurologic involvement developing in infancy with a weak cry, recurrent apnea, and myoclonic epilepsy.^{11,12} Cormier-Daire et al observed the following major clinical features, namely (1) onset in the first week of life, (2) transient hypoglycemia, (3) neurologic involvement with severe hypotonia, myoclonus epilepsy, psychomotor retardation, (4) early liver failure, and (5) a rapidly fatal course.¹¹

Key biochemical manifestations include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (> 20 and frequently > 30 mol/mol), and a raised β -hydroxybutyrate and arterial ketone body ratio of β -hydroxybutyrate to acetoacetate (> 2.0 mol/mol).⁵ Respiratory chain complex analysis of liver or muscle generally shows low activity of complex I, III, or IV. The course of the illness is usually rapidly progressive. In most of these infants, liver failure progresses to death within weeks to months after presentation, although occasional infants have recovered or have had successful liver transplantation.

A recent study suggests that antenatal manifestations are common in infants with respiratory chain disorders.¹⁵ Low birth weight (< 3 rd percentile for gestational age) was noted in 23% of cases and another 7% had other associated anomalies, including polyhydramnios, hypertrophic cardiomyopathy, cardiac rhythm abnormalities, hydronephrosis, and ventricular septal defects.¹⁵

Mitochondrial DNA Depletion Syndrome

Mitochondrial DNA depletion syndrome (MDS) is defined as a reduction in mtDNA copy number in different tissues leading to insufficient synthesis of respiratory chain complexes I, III, IV, and V.^{3,16} There are two clinical phenotypes of MDS, a myopathic and a hepatocerebral form, with considerable phenotypic heterogeneity within both forms.¹⁷ Patients with the hepatocerebral form present within the first weeks of life with hepatomegaly and progressive liver failure leading to death a few months later.^{5,6,17} Presenting symptoms include vomiting, severe gastroesophageal reflux, failure to thrive, or developmental delay.

Neurologic abnormalities include hypotonia, Leigh syndrome, nystagmus, psychomotor delay, pyramidal signs, seizures, and cataracts.^{5,6} The nystagmus is usually multidirectional, and there may be hypo- or areflexia.⁶ Other clinical features include cardiomegaly, amyotrophy, and renal tubulopathy.⁶ Biochemically, lactic acidosis, hypoglycemia, moderately raised serum alanine aminotransferase and aspartate aminotransferase, coagulopathy, and elevated total and conjugated bilirubin are common.^{5,6} Liver histology is

characterized by macro- and microvesicular steatosis, hepatocytic and canalicular cholestasis, fibrosis, and iron deposition in hepatocytes and sinusoidal cells (Fig. 2).⁶

There is considerable overlap between the clinical and laboratory features of MDS and the neonatal liver failure form of respiratory chain disease. The major difference between the two conditions is the demonstration in MDS of low ratio (< 10%) of the normal amount of mtDNA relative to nuclear DNA in affected tissues, with a normal mtDNA genome sequence (Table 3).⁶ Another difference is as compared with the neonatal liver failure of respiratory chain disease, the progression of liver failure in MDS is usually less rapid, with the course of illness lasting for a few months.⁶

Alpers-Huttenlocher Syndrome (Delayed-Onset Liver Disease)

Typically, the onset of symptoms in Alpers-Huttenlocher syndrome occurs between 2 months and 8 years of life and is characterized by hepatomegaly, jaundice, and progressive coagulopathy and hypoglycemia.¹⁸ In most of these children, liver failure is preceded by the development of hypotonia, feeding difficulties, symptoms of gastroesophageal reflux or intractable vomiting, failure to thrive, and ataxia followed by the onset of refractory partial motor epilepsy or multifocal myoclonus.^{18–20} Multiple anticonvulsants are usually necessary to control the seizures. The use of valproic acid may exacerbate the deficiency of respiratory chain enzyme activity and precipitate liver failure.¹⁹ The generally accepted diagnostic criteria of this condition are (1) presence of refractory, mixed type seizures that include a focal component, (2) episodic psychomotor regression that is often triggered by intercurrent infections, and (3) hepatopathy with or without acute liver failure.²¹

Progressive neurologic deterioration may ensue rapidly. In other children, the neurologic features are less severe or of somewhat later onset. There may be elevated blood or cerebrospinal fluid (CSF) lactate and pyruvate levels, characteristic electroencephalogram findings (high-amplitude slow activity with polyspikes),¹⁹ asymmetric abnormal visual-evoked responses,¹⁹ and low-density areas or atrophy in the occipital or temporal lobes on computed tomography (CT) scanning of the brain.²² In some patients, NADH oxidoreductase (complex I) deficiency has been found in liver or muscle mitochondria.^{11,23}

Pearson's Syndrome

Pearson's marrow-pancreas syndrome was first described in 1979 in 4 children with neonatal-onset severe macrocytic anemia, variable neutropenia and thrombocytopenia, vacuolization of marrow precursors, and ringed sideroblasts in the bone marrow.²⁴ The clinical features involve the hematopoietic system, exocrine pancreas, liver, and kidneys. Pancreatic insufficiency due to extensive pancreatic fibrosis and acinar atrophy usually causes diarrhea and fat malabsorption later in infancy or early childhood. Partial villous atrophy of the small intestine was also noted.

The liver involvement is manifested as hepatomegaly, hepatic steatosis, hemosiderosis, and cirrhosis. Liver failure and death in some cases has been reported before the age of 4 years.^{25,26} Other clinical manifestations of Pearson syndrome include renal tubular disease (Fanconi's syndrome), patchy erythematous skin lesions, and photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy.²⁷ Deletions of mtDNA segments are reported in most patients. In general, there is no effective therapy available for Pearson's syndrome apart from symptomatic treatment with red cell transfusions or carbohydrate restriction.

Villous Atrophy Syndrome

This rare disease was first described by Cormier-Daire et al²⁸ in two unrelated children with severe anorexia, vomiting, chronic diarrhea, and villus atrophy in the first year of life. Intestinal biopsy in both cases showed partial villous atrophy with eosinophilic infiltration. Both patients needed a period of parenteral nutrition because of persistence of diarrhea not responding to enteral nutrition. Significant neurodevelopment delay was noted in one of the patients. Other features included severe renal insufficiency and involvement of the pyramidal tract of the central nervous system (CNS). Hepatic involvement was characterized by mild elevation of aminotransferases, hepatomegaly, and steatosis. Diarrhea, vomiting, and lactic acidosis worsened with high dextrose intravenous infusions or enteral nutrition. Diarrhea improved and even resolved completely by 5 years of age in association with normalization of intestinal biopsies. Subsequent course of the disease was complicated by retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness with eventual death late in the first decade of life. Respiratory-chain enzyme assays were normal in circulating lymphocytes; however, complex III deficiency was demonstrated in skeletal muscle.

Navajo Neurohepatopathy

Navajo neurohepatopathy (NNH) is a sensorimotor neuropathy with progressive liver disease that has been reported in full-blooded Navajo children.¹³ This disorder was initially termed *Navajo neuropathy* because of the development of weakness, hypotonia, areflexia, loss of sensation in the extremities, acral mutilation, corneal ulceration, poor growth, short stature, and serious systemic infections.^{13,29} Cerebral magnetic resonance imaging shows the presence of progressive white matter lesions, and peripheral nerve biopsies show severe loss of myelinated fibers.^{13,29} Subsequently, it was shown that liver involvement was an important clinical feature and a common cause of death.¹³ Reye-like syndrome episodes, cholestasis, cirrhosis, or liver failure may occur in infancy or childhood. There are three clinical presentations of NNH, including an *infantile* presentation, with failure to thrive and jaundice progressing to hepatic failure and death within the first 2 years of life, with or without neurologic findings; a *childhood* form presenting between 1 and 5 years of age with rapid development of liver failure within 6 months of presentation; and the *classic* form in which progressive neurologic findings dominate although liver dysfunction (and even cirrhosis) was present in all patients. Liver histology demonstrates portal fibrosis or micronodular cirrhosis, macrovesicular and microvesicular steatosis, pseudoacinar formation, multinucleated giant cells, cholestasis, and periportal inflammation.¹³ The liver involvement is progressive with liver failure developing within months to years in most patients. There is no effective treatment to date for affected children.¹³

DIAGNOSIS OF MITOCHONDRIAL HEPATOPATHIES

When to Suspect Mitochondrial Hepatopathies?

Diagnosis of mitochondrial respiratory chain disorders in patients with liver disease requires a high index of suspicion. Clinical events that should suggest these disorders include (1) association of neuromuscular symptoms with liver dysfunction, (2) multisystem involvement in a patient with acute or chronic liver disease, (3) rapidly progressive course of liver disease, and (4) presence of lactic acidosis, hepatic steatosis, or ketonemia.² Table 4 shows screening tests available for respiratory chain defects. Lactic acidemia is a well-known feature of mitochondrial disorders, including mitochondrial hepatopathies.³⁰ The pathogenesis of lactic acidemia lies in the fact that all cells use glucose and produce pyruvate by glycolysis.³¹ The pyruvate is then reduced by NADH to lactate, if the mode of metabolism is preferentially glycolytic or if there is a problem reoxidizing NADH.^{3,30}

Reoxidation of NADH generated by pyruvate dehydrogenase complex is performed by respiratory chain complex within mitochondria.³⁰

Lactic acidemia is a constant presenting feature in some, intermittent in others, and may be absent in yet other mitochondrial disorders.³⁰ The majority of respiratory chain defects presents with a raised blood and CSF lactate associated with a raised lactate to pyruvate ratio, indicating altered cellular redox state.³⁰ Lactic acidemia is prominent in neonatal liver failure, MDS, and villous atrophy syndrome but generally not present in Navajo neurohepatopathy and Alpers-Huttenlocher syndrome (Table 3). More specifically, Robinson³⁰ points out that moderate lactic acidemia (defined as serum lactate level between 2 and 5 mmol/L) is noted in MDS caused by mutations of the genes *DGUOK*, *TK2*, and *POLG*, and severe lactic acidemia (serum lactate more than 5 mmol/L) is a relatively constant feature in *BCS1L* mutations affecting complex III.³⁰

Measurement of Mitochondrial Respiration

One sensitive method of documenting altered mitochondrial function is the direct measurement of mitochondrial respiration. Analysis of oxygen consumption in fresh mitochondrial-enriched fractions of tissues (liver, muscle, lymphocytes, fibroblasts) can be performed by polarographic studies in the presence of a series of respiratory substrates to define the site of the respiratory impairment.² For example, patients with complex I deficiency (NADH oxidoreductase) will show impaired mitochondrial oxygen consumption stimulated by NADH substrates, such as glutamate and malate, and those with complex II (succinate oxidoreductase) deficiency will have improved respiration with FADH substrates, such as succinate.² These tests require isolation of mitochondria from fresh tissue, which is not available at most centers.

Enzymatic Activity of Respiratory Chain Complexes

Alternatively, direct measurement of the enzymatic activity of each of the complexes of the mitochondrial respiratory chain can be measured in frozen tissues. Samples of liver, kidney, myocardium, skin, or other tissues must be frozen immediately at the bedside or in the operating room and stored at -80°C . Measurement of respiratory chain enzyme activities can be performed spectrophotometrically using specific electron acceptors and donors.³²

Histopathologic Investigations

All forms of mitochondrial hepatopathies show abnormal hepatic histopathologic features, which include micro- and macrovesicular steatosis, cholestasis, hepatocellular degeneration and swelling, lobular inflammation, portal fibrosis, and eventually cirrhosis. Pseudoacinar formation is noted to be prominent in NNH,¹³ and hemosiderosis of the liver is noted in Pearson's syndrome^{25,26} and MDS.¹⁷

GENETICS OF MITOCHONDRIAL HEPATOPATHIES

More than 200 pathogenic point mutations, deletions, insertions, and rearrangements have been identified since the first mtDNA mutations were reported in 1988, and are more likely to be associated with neuromuscular disorders than hepatic.³³ On the contrary, it is now clear that most mitochondrial diseases with primary involvement of the liver are caused by nuclear, rather than mtDNA mutations (Table 3).

Neonatal Liver Failure

Low hepatic activity of respiratory chain complexes IV, I, III, and occasionally of complex II, either in isolation or in combination, has been found in infants with this presentation.^{11,34,35} Among these, deficiency of complex IV (cytochrome *c* oxidase; COX)

is the most common cause. COX is the terminal enzyme of the mitochondrial respiratory chain that catalyzes the transfer of reducing equivalents from cytochrome *c* to molecular oxygen (Fig. 1).³⁶ This exergonic reaction is coupled with COX-mediated proton translocation from matrix to cytosol.³⁶ The mammalian COX is a hetero-oligomer composed of 13 subunits. The 3 largest subunits forming the catalytic core of the enzyme are encoded by mtDNA, whereas the remaining 10 subunits involved in the assembly and regulation of the enzyme are encoded by nuclear DNA.³⁶

SCO1 GENE

In one affected family with predominately hepatic failure in infancy, lactic acidosis and neurodevelopmental delays, mutations in the COX assembly nuclear gene *SCO1* have been associated with COX deficiency.³⁷ The *SCO1* gene, located at chromosome 17p13.1, is believed to encode a protein functioning as a copper chaperone that transfers copper from Cox17p, a copper-binding protein of the cytosol and mitochondrial intermembrane space, to the mitochondrial COX subunit II.³⁸ Mutation analysis of affected patients in a family showed compound heterozygosity for the *SCO1* gene.³⁷ A mutated allele inherited from the father showed a 2-bp frameshift deletion (Δ GA; nt 363–364) resulting in both a premature stop codon and a highly unstable mRNA. The maternally inherited mutation (C520T) changed a highly conserved proline into a leucine in the protein (P174L).³⁷ This proline, adjacent to the CxxxC copper-binding domain of *SCO1*, is likely to play a crucial role in the tridimensional structure of the domain.

BCS1 GENE

Respiratory complex III (ubiquinol–cytochrome *c* reductase complex) catalyzes the electron transfer from coenzyme Q to cytochrome *c*. *BCS1L* is a nuclear gene encoding proteins involved in the assembly of respiratory complex III. A mutation in *BCS1L* has been found to be associated with mitochondrial neonatal liver failure.³⁹ De Lonlay et al³⁹ reported deficient activity of complex III of the respiratory chain in liver, fibroblasts, or muscle in affected infants with hepatic failure, lactic acidosis, renal tubulopathy, and variable degrees of encephalopathy. Three mutations in *BCS1L* were demonstrated in three affected families.³⁹ Subsequently, de Meirleir et al⁴⁰ confirmed that mutations in *BCS1L* were associated with fatal complex III deficiency and liver failure in two siblings. These included a missense mutation R45C and a nonsense mutation R56X, both located in the exon 1 of *BCS1L* gene.⁴⁰ It is likely that mutations in *BCS1L* will be responsible for a substantial portion of infants who present with neonatal liver failure and lactic acidosis. It should be noted, however, that not all patients with neonatal liver failure will have a positive identification of a mutation.³⁹ Other genetic causes are likely to be identified in the future.

mtDNA Depletion Syndrome

The mtDNA processing enzyme activities are dependent on several factors, including deoxyribonucleotide (dNTP) concentrations within the mitochondria, availability of ATP, and several metal cofactors.⁴¹ Imbalance of any of these cofactors or enzymes could affect mtDNA stability. The mtDNA pool is maintained by either import of cytosolic dNTPs through dedicated transporters or by salvaging deoxynucleosides within the mitochondria. The mitochondrial deoxynucleoside salvage pathway is regulated by nuclear-encoded enzymes, including deoxyguanosine kinase (dGK) and thymidine kinase-2 (TK2).^{42,43} Human dGK phosphorylates deoxyguanosine and deoxyadenosine, whereas TK2 phosphorylates deoxythymidine, deoxycytidine, and deoxyuridine. Imbalance of this mitochondrial dNTP pool has been proposed to be responsible for both the hepatocerebral and myopathic forms of MDS.⁴⁴ In 2001, mutations in two genes involved in this pathway

were identified in patients with MDS: *DGUOK* in the hepatocerebral form and *TK2* in the myopathic form.^{44,45}

DGUOK

Mandel et al,⁴⁴ using homozygosity mapping in three consanguineous kindreds affected with hepatocerebral MDS, mapped this disease to chromosome 2p13, which encompasses the gene *DGUOK* encoding dGK. A single-nucleotide deletion (204delA) within the coding region of *DGUOK* was identified.⁴⁵ Reduction of enzymatic activities of mitochondrial respiratory chain complexes containing mtDNA encoded subunits (complexes I, III, and IV, but not complex II, which is solely encoded by nuclear genes) was demonstrated in the liver but not in muscle, showing the tissue-specific nature of this disorder. However, Salviati et al⁴⁶ screened the frequency of *DGUOK* mutations in 21 patients with hepatocerebral MDS and noted that *DGUOK* mutations were present in only 14%, suggesting this was not the only gene responsible for MDS in the liver.⁴⁶ No genotype-phenotype correlation was demonstrated.

In recent years, 2 other nuclear genes have been identified as additional causes of the hepatocerebral form of MDS. Mutations in DNA polymerase- γ (*POLG*), the mitochondrial polymerase that is encoded by a nuclear gene, have now been described in infants with MDS as well as older children with Alpers-Huttenlocher disease.^{47,48} Most of the cases with MDS in early childhood are associated with at least one mutation in the linker region of *POLG* and one in the polymerase domain. More recently, Spinazzola et al⁴⁹ have employed an integrative genomics approach to discover mutations in the nuclear gene *MPV17* in three families affected by the hepatocerebral form of MDS. This gene encodes an inner mitochondrial membrane protein of uncertain function.

Alpers-Huttenlocher Syndrome

Mutations in *POLG* have recently been shown to be the primary genetic cause of Alpers-Huttenlocher syndrome.^{50,51} DNA polymerase- γ (pol- γ) is essential for mtDNA replication and repair,⁵² is comprised of a 140-kDa catalytic (α) subunit that contains DNA polymerase, 3'-5' exonuclease, and dRP lyase activities, and a 55-kDa accessory (β) subunit that functions as a processivity and DNA binding factor.⁵² Deficiency in mitochondrial pol- γ activity and mtDNA depletion was first reported in a patient with Alpers-Huttenlocher syndrome by Naviaux et al in 1999.⁵³ Subsequently, Naviaux et al⁵⁰ reported that in two unrelated pedigrees with Alpers-Huttenlocher syndrome, each affected child was found to harbor a homozygous mutations in exon 17 of *POLG* that led to a Glu873Stop mutation just upstream of the polymerase domain of the protein. In addition, each affected child was heterozygous for the G1681A mutation in exon 7 that led to an Ala467Thr substitution in pol- γ , within the linker region of the protein.⁵⁰ Subsequently, other reports have confirmed that the Ala467Thr substitution in pol- γ was the most common although not exclusive, mutation in Alpers-Huttenlocher syndrome.^{47,48}

Molecular diagnosis is now possible in the majority of Alpers-Huttenlocher syndrome patients.⁵¹ Nyugen et al⁵¹ sequenced the *POLG* locus in 15 sequential probands with the clinical features of Alpers-Huttenlocher syndrome and noted that *POLG* DNA testing accurately diagnosed 87% of cases. Five new *POLG* amino acid substitutions (F749S, R852C, T914P, L966R, L1173fsX) were reported. The most common mutation was the Ala467Thr substitution described above, which accounted for ~40% of the alleles and was present in 65% of the patients.⁵¹ All patients with Alpers-Huttenlocher syndrome had either Ala467Thr or the W748S substitution in the linker region. Mutations in *POLG* have also been associated with another severe form of hepatocerebral syndrome, autosomal dominant

or recessive progressive external ophthalmoplegia, neuropathy, ataxia, hypogonadism, migraine, hearing loss, muscle weakness, parkinsonism, and psychiatric symptoms.^{48,50,54}

Navajo Neurohepatopathy and *MPV17* Gene Mutation

Vu et al⁵⁵ first demonstrated mtDNA depletion in liver tissue of two patients with NNH, suggesting that a nuclear gene might be responsible for this autosomal recessive disease. A genome-wide scan, performed using 400 DNA microsatellite markers demonstrated mapping of the disease to chromosome 2p24.1.⁵⁵ *MPV17*, the gene associated with MDS, was recently mapped to this region. The *MPV17* product is involved in mtDNA maintenance and in the regulation of OXPHOS⁴⁹ and is localized to the inner mitochondrial membrane.⁴⁹ Sequencing of *MPV17* in 6 NNH patients from 5 families in 2006 demonstrated the same homozygous disease-causing R50Q mutations in exon 2 in all patients, confirming a founder effect in this disease.⁵⁶ Thus, it is now clear that NNH is indeed a form of mtDNA depletion with a unique clinical presentation in Navajos. Molecular diagnosis, which is now available in CLIA-approved clinical laboratories, may now play a role in differentiating this cause of neonatal liver disease from other causes in Navajo children.

Pearson's Syndrome

The association of Pearson's syndrome and a specific deletion in mtDNA was first reported in 1990 by Rotig et al.⁵⁷ It is now established that mtDNA rearrangements are present in all patients with this rare disease with large (4000–5000 base-pair) deletions predominating in three quarters of reported cases.^{25,58,59} The most common deletion is located between nt 8488 and nt 13,460.⁶⁰ The proteins affected by this deletion included respiratory chain enzymes (complex I is the most severely affected), 2 subunits of complex V, 1 subunit of complex IV, and 5 t-RNA genes. Other mtDNA deletions of differing lengths are associated with clusters of the characteristic clinical manifestations.^{57,59} Rotig et al⁵⁷ reported a 5-year-old boy with sideroblastic anemia, persistent diarrhea, lactic acidosis, and liver failure with a 3.1-kb deletion (nt 6074–9179). In contrast, Jacobs et al⁵⁹ described a patient with anemia and diarrhea but no pancreatic or hepatic involvement with a 3.4-kb deletion (nt 6097–9541). Heteroplasmy of mtDNA in different tissues may explain these discrepant findings.

More recently, Muraki et al⁶¹ described a child with classic features of Pearson's syndrome. Initial analysis for mtDNA deletions or duplications on bone marrow at 1 year of age, and a repeat analysis on the muscle at 5 years of age, did not show any duplication. An analysis after the death of the child at 7 years of age showed mtDNA duplications in the kidneys, heart, and bone marrow. The authors concluded that mtDNA duplications are present in many tissues but may fluctuate in the bone marrow.⁶¹

Villous Atrophy Syndrome

Villous atrophy syndrome has been recognized as a mtDNA rearrangement defect.²⁸ A complex III deficiency was found in muscle of affected patients. Southern blot analysis showed evidence of heteroplasmic mtDNA rearrangements that involved deletion and deletion-duplication.²⁸ Two different mutations were described in the 2 children reported.²⁸ In one patient, a deletion spanning 3380 base pairs encompassed 3 genes for complex I and 3 transfer ribonuclease genes. The deletion in the second patient was larger.

MEDICAL THERAPIES OF MITOCHONDRIAL HEPATOPATHIES

Treatment of acute liver failure and progressive liver disease in the mitochondrial hepatopathies include medical therapies and liver transplantation. Current medical therapies (Table 5) involved the use of various vitamins, cofactors, respiratory substrates, or antioxidant compounds with the aim of mitigating, postponing, or circumventing the damage

to the respiratory chain.^{2,62} Unfortunately, none of these therapies has been proved to be effective in the majority of patients.⁶³ Clinical management of individuals with the respiratory chain disorders is thus largely supportive with the aims of providing prognostic information and genetic counseling.

Based on the understanding of the enzymatic and biochemical derangements, several treatment strategies have been proposed for mitochondrial disorders, though none have been proved to be effective.^{63,64} Several different pharmacologic treatments and nutritional supplements have been used in individuals with mitochondrial disorders with varying degree of success. These include antioxidants (vitamin E, vitamin C),^{65,66} electron acceptor and cofactors (coenzyme Q₁₀, idebenone, thiamine, riboflavin, menadione),⁶⁷⁻⁷³ and agents to specifically treat lactic acidosis (dichloroacetate).⁷⁴ Other agents proposed include succinate, which donates electron directly to complex II⁷⁵; carnitine, which can correct secondary carnitine deficiency⁷⁶; and creatine monohydrate, which enhances muscle phosphocreatine.⁷⁷ Other supportive treatments may also include infusion of sodium bicarbonate for acute metabolic acidosis, transfusion for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency.²

A recent Cochrane analysis concluded that there is no clear evidence to suggest the benefit of any medical therapies in mitochondrial disorders.⁶³ However, it should be noted that most of the therapeutic trials reported were conducted primarily in the myopathic forms of mitochondrial disorders.⁶³ There is little reported experience on medical therapies in mitochondrial hepatopathies.

LIVER TRANSPLANTATION

The role of liver transplantation (LT) in mitochondrial hepatopathies is complicated because of the multisystemic nature of this disorder and the observation that involvement of other organ systems may not become evident until after liver transplantation.^{79,80} Summarizing the reported experience, survival appears to be less than 50%.⁷⁹⁻⁸² Clearly the presence of significant neuro-muscular or cardiovascular involvement at the time of LT evaluation is an absolute contraindication to LT as a therapeutic option, inasmuch as extrahepatic clinical disease continues to progress to death after transplantation.^{79,80} It also appears that significant intestinal symptomatology (and hence presumed intestinal involvement) predicts a poor prognosis after LT.⁷⁹ Finally, and most worrisome, unrecognized neurologic involvement prior to transplantation may progress rapidly after transplantation.⁸⁰ Thus, the absence of extrahepatic features of mitochondrial disease at the time of LT does not guarantee a good outcome even if the transplant is successful.

There have been, however, patients who have had successful LT with no development of posttransplant extrahepatic manifestations. Thus, a careful and thorough pretransplant evaluation of potentially affected organ systems (kidneys, heart, muscle, intestinal tract, central nervous system, and pancreas) is mandatory. To exclude mitochondrial hepatopathies in patients with neonatal acute liver failure, Thomson et al⁸⁰ proposed a protocol of investigations that includes blood (plasma lactate, postprandial 3-OH-butyrate, free fatty acid/ketones body ratio), liver and muscle biopsies, CSF lactate, tubular reabsorption of phosphate, fasting urine osmolality, echocardiogram, electroretinogram, and cranial CT scan. However, performing such evaluation is particularly challenging in patients presenting with acute liver failure and associated acute neurologic decompensation in whom a decision about LT needs to be made urgently, sometimes before diagnostic testing can be completed. Therefore, improved diagnostic techniques and predictive biomarkers to assist with selecting the best candidates for LT are certainly needed.

GAPS IN CURRENT KNOWLEDGE

Despite elucidation of the genetic etiology of mitochondrial hepatopathies in recent years, there remains much to be learned about these disorders. The overall frequency and full clinical spectrum of hepatic involvement and natural history need to be defined. Diagnostic evaluation now involves genotyping the likely involved genes; however, more rapid and predictable diagnostic techniques (e.g., needle liver and muscle biopsy analysis of respiratory chain enzymes) still need to be developed and made widely accessible. Genotype-phenotype correlations and the relationship of genotype to response to liver transplantation await prospective large-scale studies. There are also undoubtedly other genetic causes that will be identified in coming years. A feasible and effective treatment is, at present, not available and the precise role of liver transplantation needs to be better defined. Finally, the role of polymorphisms in genes causing these disorders as potential modifiers in other disorders of the liver may identify new targets for therapeutic approaches. The Cholestatic Liver Disease Consortium, a National Institutes of Health funded, multicentered Rare Disease Clinical Research Consortium,⁸³ is attempting to address many of these questions.

Acknowledgments

Way S. Lee was a visiting Fulbright Scholar from the Department of Pediatrics, University of Malaya Medical Centre, Kuala Lumpur, Malaysia, to the Section of Pediatric Gastroenterology, Hepatology, and Nutrition, The University of Colorado School of Medicine, and The Children's Hospital, Denver, Colorado. This work was supported in part by grants from the National Institutes of Health (MOI RR00069, ROI DK038446, U01DK062453, U54DK078377) and the Fulbright Scholarship.

ABBREVIATIONS

AFLP	acute fatty liver of pregnancy
ATP	adenosine triphosphate
BCS1L	cytochrome bc synthesis 1L
CNS	central nervous system
COX	cytochrome <i>c</i> oxidase
CSF	cerebrospinal fluid
CT	computed tomography
dGK	deoxyguanosine kinase
DGUOK	deoxyguanosine kinase gene
dNTP	deoxyribonucleotide
dRP	deoxy-ribose phosphate
ETF	electron transfer flavoprotein
FADH₂	reduced flavin adenine dinucleotide
LCHAD	long-chain 3-hydroxyacyl CoA dehydrogenase
LT	liver transplantation
MDS	mitochondrial DNA depletion syndrome
MPV17	mitochondrial inner membrane protein gene
MRI	magnetic resonance imaging

mtDNA	mitochondrial DNA
NADH	reduced nicotinamide adenine dinucleotide
NNH	Navajo neurohepatopathy
nt	nucleotide
OXPHOS	oxidative phosphorylation
POLG	DNA polymerase- γ gene
pol-γ	DNA polymerase- γ
SCO1	suppressor of cytochrome oxidase deficiency 1
TK2	thymidine kinase 2
TK2	thymidine kinase 2 gene
TP	thymidine phosphorylase
TPGS	D- α -tocopheryl polyethylene glycol-1000 succinate
t-RNA	transfer RNA

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Figure 1.

The respiratory chain protein complexes and oxidative phosphorylation of the mitochondria. Reducing equivalents derived from glycolysis, fatty acid oxidation, and the tricarboxylic acid cycle are converted into ATP through a system of electron carriers (protein complexes I through IV, coenzyme Q, and cytochrome *c*) in the inner mitochondrial membrane, via the efficient transport of electrons down this chain. This results in the generation of a transmembrane proton gradient that drives the synthesis of ATP by complex V (not shown). ETF, electron transfer flavoprotein; cplx, complex; cyt, cytochrome.

Figure 2.

(A) Photomicrograph of liver biopsy from a 3-month-old child with *POLG* mutations and mitochondrial DNA depletion syndrome, showing microvesicular steatosis, cholestasis with bile pigment in canaliculi (arrows), and ballooning degeneration of hepatocytes (H&E stain, magnification, $\times 200$). (B) Electron micrograph from the same patient showing small vesicles of lipid and pleomorphic, distorted mitochondria (magnification, $\times 13,700$).

Table 1**Classification of Mitochondrial Hepatopathies****Primary disorders**

1. Electron transport (respiratory chain) defects
 - Neonatal liver failure
 - Complex I deficiency
 - Complex IV deficiency (*SCO1* mutations)
 - Complex III deficiency (*BCS1L* mutations)
 - Multiple complex deficiencies
 - Mitochondrial DNA depletion syndrome (*DGUOK*, *MPV17*, *POLG* mutations)
 - Delayed-onset liver failure: Alpers-Huttenlocher syndrome (*POLG* mutations)
 - Pearson's marrow-pancreas syndrome (mtDNA deletion)
 - Mitochondrial neuro-gastrointestinal encephalomyopathy (*TP* mutations)
 - Chronic diarrhea (villus atrophy) with hepatic involvement (complex III deficiency)
 - Navajo neurohepatopathy (mtDNA depletion; *MPV17* mutations)
 - Electron-transfer flavoprotein (ETF) and ETF-dehydrogenase deficiencies
2. Fatty acid oxidation and transport defects
 - Long-chain hydroxyacyl CoA dehydrogenase deficiency
 - Acute fatty liver of pregnancy (AFLP; LCHAD enzyme mutations)
 - Carnitine palmitoyltransferase I and II deficiencies
 - Carnitine-acylcarnitine translocase deficiencies
 - Fatty acid transport defects
3. Disorders of mitochondrial translation process
4. Urea cycle enzyme deficiencies
5. Phosphoenolpyruvate carboxykinase deficiency (mitochondrial)

Secondary disorders

1. Reye's syndrome
2. Hepatic copper overload
 - Wilson's disease
 - Indian childhood cirrhosis
 - Idiopathic infantile copper toxicosis
 - Cholestasis
3. Hepatic iron overload
 - Hereditary hemochromatosis, juvenile hemochromatosis
 - Neonatal iron storage disease
 - Tyrosinemia, type I
 - Zellweger syndrome
4. Drugs and toxins
 - Drugs: valproic acid, salicylic acid, nucleoside analogues (fialuridine, 2',3'-dideoxyinosine, azidothymidine), amiodarone, tetracycline, chloramphenicol, barbiturates
 - Chemical toxins: iron, ethanol, cyanide, antimycin A, rotenone, others
 - Bacterial toxins: cerulide (*Bacillus cereus* emetic toxin), Ekiri
5. Conditions causing mitochondrial lipid peroxidation

- Cholestasis
- Hydrophobic bile acid toxicity (cholestasis, bile acid synthesis, and canalicular transport defects)
- Nonalcoholic fatty liver disease and steatohepatitis—associated with obesity, insulin resistance, diabetes mellitus, drugs, parenteral nutrition, bacterial contamination of small bowel, jejuno-ileal bypass, or idiopathic

6. Cirrhosis

Adapted with permission from SokolRJ, Treem WR. Mitochondria and childhood liver diseases. *J Pediatr GastroenterolNutr* 1999;28:4-16.

Table 2**Clinical and Laboratory Features of Primary Mitochondrial Hepatopathies**

Disorder	Onset	Age at Onset	Liver Disease	Extrahepatic Features	Plasma L/P Ratio	Seizures	Lactate
Neonatal liver failure	Acute	Early neonatal	Neonatal liver failure	Lethargy, vomiting, poor suck from birth, apnea, hypotonia	±	↑	↑
mtDNA depletion	Acute/chronic	Early neonatal	Hepatomegaly, progressive liver failure Death within a few months	FTT, poor feeding, psychomotor delay, nystagmus, pyramidal signs Less common: cardiomegaly, tubulopathy	+	↑	↑
Delayed-onset liver disease (Alpers)	Insidious	Children and young adults	Hepatomegaly, jaundice, raised liver enzymes, cirrhosis, and progressive liver failure	Liver failure preceded by neurologic symptoms, psychomotor regression, vomiting Partial motor epilepsy or multifocal myoclonus, characteristic EEG	++	Normal	Normal
Pearson's syndrome	Insidious	Infancy	Hepatomegaly, cholestasis, raised liver enzymes, progressive liver failure Death in early childhood	Refractory sideroblastic anemia, vacuolization of marrow precursors, variable neutropenia and thrombocytopenia	—	Normal or ↑	Normal or ↑
Villous atrophy syndrome	Chronic	Early childhood	Hepatomegaly, raised liver enzymes	Vomiting, anorexia, chronic diarrhea, villous atrophy, diabetes mellitus, cerebellar ataxia, sensorineural deafness, retinitis pigmentosa, seizures	±	↑	↑
Navajo neurohepatopathy	Acute or chronic	Infancy to childhood	Jaundice, ascites, Reye's syndrome-like episodes, progressive cirrhosis, and liver failure Death in early childhood	Sensorimotor neuropathy, corneal anesthesia, acral mutilation, progressive CNS white matter lesions	—	±	±

++ , present always; ±, occasionally present; —, not present; EEG, electroencephalogram; CNS, central nervous system; FTT, failure to thrive; ↑, increased; L/P ratio, molar ratio of plasma lactate/pyruvate concentration.

Table 3**Respiratory Chain Complex-Involved and Molecular Causes of Mitochondrial Hepatopathies**

Disorder	mtDNA	Respiratory Chain Complex Involved	Gene	Protein	Functions	References
Nuclear genes						
Neonatal liver failure	Normal	IV	<i>SCO1</i>	Copper chaperone of complex IV (cytochrome <i>c</i> oxidase)	Transfers copper from Cox17p to COX subunits I and II	37
		III	<i>BCS1L</i>	An assembly protein of complex III (ubiquinol–cytochrome <i>c</i> reductase)	Catalyzes the electron transfer from coenzyme Q to cytochrome <i>c</i>	38–40
mtDNA depletion syndrome	Depletion	I, III, IV	<i>POLG</i>	Mitochondrial DNA polymerase- γ (pol- γ)	pol- γ activity is essential for mtDNA replication and repair. Defective pol- γ leads to mtDNA depletion	41
		I, III, IV	<i>DGUOK</i>	dGK, mitochondrial nucleotide salvaging	dGK, together with TK2, functions to maintain supply of dNTPs for mtDNA synthesis	43–46
		I, III, IV	<i>MPV17</i>	Mitochondrial inner membrane protein	mtDNA maintenance and regulation of OXPHOS; absence or malfunction causes OXPHOS failure and mtDNA depletion	49
Alpers-Huttenlocher syndrome	Normal	I	<i>POLG</i>	See above	See above	50–53
Navajo Neurohepatopathy	Depletion	I, III, IV	<i>MPV17</i>	See above	See above	55, 56
mtDNA						
Pearson's syndrome	Deletion	I, III	mtDNA deletion	Synthesis of complex III, I	Deficiencies of complex III, I	58, 59
Villous atrophy syndrome	Rearrangement	III	mtDNA rearrangement	Synthesis of complex III	Deficiency of complex III	28

Table 4**Screening Tests for Respiratory Chain Defects**

Plasma lactate > 2.5 mmol/L (persistently elevated)
Molar ratio of plasma lactate/pyruvate > 20:1 mol/mol
Molar ketone body ratio: arterial 3-hydroxybutyrate/ acetoacetate > 2:1 mol/mol
Paradoxical increase in plasma ketone bodies or lactate after meals
Oral glucose load (2 g/kg): repeat plasma lactate/pyruvate testing each 15 minutes for 90 minutes; elevated lactate/pyruvate ratio
Urine lactate, succinate, fumarate, malate, 3 methylglutaconic, 3-methylglutaric by gas chromatography-mass spectroscopy

Adapted with permission from SokolRJ, Treem WR. Mitochondria and childhood liver diseases. J Pediatr Gastroenterol Nutr 1999;28:4-16.

Table 5**Proposed Pharmacologic Treatments for Respiratory Chain Disorders**

Pharmacologic Treatments		Dosage	References
Electron acceptors and cofactors			
Coenzyme Q ₁₀	Redox bypass of complex I; free radical scavenger (antioxidant)	Adult: 60-300 mg/day * Ped: 3-5mgkg ⁻¹ day ⁻¹	67-70
Idebenone	Redox bypass of complex I; free radical scavenger (antioxidant)	Adult: 90-270 mg/day * Ped: 5 mg kg ⁻¹ day ⁻¹	71
Thiamine (vitamin B ₁)	Cofactor of pyruvate dehydrogenase	Adult: 150-300 mg/day	72
Riboflavin (vitamin B ₂)	Acts as flavin precursor for complexes I and II	Adult: 50-200 mg/day	73
Menadione (vitamin K ₃)	Bypass complex III (with vitamin C)	Adult: 40-160 mg/day	78
Antioxidants			
Vitamin E (TPGS)	Antioxidant	Adult: 400-800 IU/day * Ped: 25 IU kg ⁻¹ day ⁻¹	65
Ascorbic acid (vitamin C)	Antioxidant	Adult: 2-4 g/day	66
Other mechanisms			
Succinate	Donates electrons directly to complex II	Adult: 6-16 g/day	75
Carnitine	Replace secondary carnitine deficiency	Adult: up to 3 g/day * Ped: 50-100 mg kg ⁻¹ day ⁻¹	76
Creatine monohydrate	Enhances muscle phosphocreatine	Adult: up to 10 g/day * Ped: 0.1-0.2 g kg ⁻¹ day ⁻¹	77
Dichloroacetate	Reduces lactic acidosis by enhancing pyruvate dehydrogenase activity	Adult: 25 mg kg ⁻¹ day ⁻¹ * Ped: 25-50 mg kg ⁻¹ day ⁻¹	74

Adapted from Gillis LA, SokolRJ. Gastrointestinal manifestations of mitochondrial disease. Gastroenterol Clin North Am 2003;32:789-817. TPGS, D-α-tocopheryl polyethylene glycol-1000 succinate.

* Pediatric (Ped) doses are estimates and have NOT been subjected to clinical dosage trials.