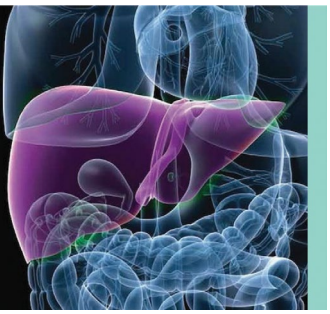

Mitochondrial Hepatopathies

*Hana Alharbi, M.D., *,†,# Jessica R.C. Priestley, M.D., Ph.D., *,#*
*Benjamin J. Wilkins, M.D., Ph.D.,‡ and Rebecca D. Ganetzky, M.D. *,§,¶*

PRETEST

1. What clinical features should increase suspicion for underlying mitochondrial hepatopathy?
2. How are mitochondrial hepatopathies diagnosed?
3. How are mitochondrial hepatopathies treated?

Mitochondria play critical roles in energy, calcium, iron, and reduction/oxidation homeostasis, as well as regulation of apoptosis. They are the only organelle that contains its own circular genomes (mitochondrial DNA [mtDNA]). Maternally inherited mtDNA houses 37 genes encoding mitochondrial transfer RNAs (tRNAs), ribosomal RNA, and 13 proteins that exclusively function as subunits of the oxidative-phosphorylation machinery. Additional proteins critical to mitochondrial structure and function are encoded by the nuclear genome.

Mitochondrial disorders include defects in oxidative-phosphorylation complexes, mtDNA maintenance, and mtDNA transcription and translation and can result from mitochondrial or nuclear mutations and yield disease involving virtually every organ system, including the liver. Mitochondrial hepatopathies are heterogenous and individually rare, but collectively they comprise an important cause of early liver failure. In two studies of infants with acute liver failure, about 20% of cases were attributable to mitochondrial pathology.[1,2]

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CoA, coenzyme A; CSF, cerebrospinal fluid; DLD, dihydrolipoamide dehydrogenase; FFT, failure to thrive; GRACILE, growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death; MDS, mitochondrial depletion syndrome; MMA, methylmalonic acid; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; PMIM, Phenotype Mendelian Inheritance in Man; tRNA, transfer RNA.

From the *Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA; †Department of Pediatrics, University of Tabuk, Tabuk, Saudi Arabia; ‡Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; §Mitochondrial Medicine Frontier Program, Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA; and ¶Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

#These authors contributed equally to this work.

This work was supported by R.D.G. consults for Minovia Therapeutics and received grants from National Institute of Diabetes and Digestive and Kidney Diseases (DK113250).

Potential conflict of interest: Nothing to report.

Received February 22, 2021; accepted April 25, 2021.

View this article online at wileyonlinelibrary.com

CLINICAL FEATURES

Mitochondrial liver disease may manifest as liver failure (acute, chronic, or recurrent), cholestasis, liver fibrosis, or elevated transaminases (Table 1). Presentation is typically pediatric. A mitochondrial etiology is especially likely in cases with multisystem involvement but is also associated with isolated hepatopathy. Low birth weight and intrauterine growth restriction have been associated.[3,4] Lactic acidosis and hypoglycemia are common biochemical features[5,6] and could lead to the misdiagnosis of other conditions, such as glycogen storage disease type I.[6]

Mitochondrial depletion syndromes (MDSs) feature decreased mtDNA copy number secondary to defects in mtDNA replication. MDSs may present with infantile hepatocerebral syndrome with acute or chronic liver failure. Mortality is high. Hepatocellular carcinoma is a complication in survivors (*DGUOK* and *MPV17*).[4,5] Affected infants typically present with growth failure, feeding difficulty, developmental delay, and hypotonia. Although brain involvement is usually prominent, in rare cases *DGUOK* may cause isolated liver failure. In *POLG* disease, brain involvement may not be immediately apparent, but developmental regression and epilepsia partialis continua are inevitable. Valproate triggers fulminant liver failure in MDS[7] and is contraindicated. Pediatric valproate-induced liver failure should be assumed to be MDS. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) secondary to thymidine phosphorylase deficiency is an adolescent-onset MDS that may have cirrhosis, as well as gastrointestinal dysmotility, peripheral neuropathy, and asymptomatic leukoencephalopathy.[8]

Single large-scale mtDNA deletions cause a spectrum of phenotypes, including Pearson syndrome, a severe disease characterized by sideroblastic anemia and exocrine pancreatic insufficiency. More than 33% of patients have liver involvement (hepatomegaly, cholestasis, and/or progressive liver failure). Kearns-Sayre syndrome develops in childhood in survivors. Point mutations in mtDNA almost never cause liver disease.[9]

Mitochondrial translation disorders are also characterized by early-onset liver failure with frequent neurological manifestations. Early diagnosis and management are critical because recovery is possible with appropriate medical support, for example, acute infantile liver failure caused by mutations in *TRMU*.[6] Mitochondrial hepatopathy is also associated with deficiency of individual oxidative-phosphorylation complexes, for example, *BCS1L* mutations cause infantile cholestasis with liver iron overload and multisystemic features.[4]

WORK-UP/DIAGNOSIS

Diagnostic work-up for suspected mitochondrial hepatopathy includes full phenotyping, biochemical studies, functional studies, and genetic confirmation.[10] Cardiac, neuromuscular, retinal, or auditory involvement may raise suspicion for mitochondrial disease generally, but specific features may be diagnostic. Peripheral neuropathy (*MPV17*), pili torti (*BCS1L*), rotary nystagmus (*DGUOK*), and sideroblastic anemia (mtDNA deletion) can be observed (Fig. 1). Biochemical laboratory testing, including amino acids, organic acids, and lactate/pyruvate and acylcarnitine profiles, are not sensitive but can strongly increase suspicion for mitochondrial disease.

Pathological examination of liver tissue plays a key role in confirming a clinical suspicion of mitochondrial hepatopathy and directing future testing (Fig. 2). Light microscopic findings are variable and depend on genetic lesion, patient age, and disease severity at time of biopsy. Classical findings beyond early infancy include nonzonal mixed (macrovesicular and microvesicular) steatosis, variable fibrosis, and presence of oncocytic hepatocytes with granular, hypereosinophilic cytoplasm. Electron microscopy shows this oncocytic change reflects proliferation of structurally abnormal mitochondria, characterized by lack of cristae, tubular cristae, and/or electron-dense matrix granules. The light microscopic differential diagnosis includes other metabolic disorders, Wilson disease, and secondary mitochondrial dysfunction as a result of drug toxicity; ultrastructural changes, including mitochondrial proliferation, are more specific for primary mitochondrial disorders.

Mitochondrial hepatopathy is also a significant causative factor for congenital liver failure, where the histological picture may be of neonatal (giant cell) hepatitis, or even so-called neonatal hemochromatosis: hepatic parenchymal collapse with massive ductular proliferation, cholestasis, and evidence of siderosis both in liver and extrahepatic tissues. In such cases, classic histological and ultrastructural features may be absent; ancillary testing of rapidly procured postmortem tissue is required to establish the diagnosis. The differential diagnosis in these cases includes gestational alloimmune liver disease, congenital infection, or other metabolic disorders.

TABLE 1. MITOCHONDRIAL DISORDERS ASSOCIATED WITH HEPATOPATHY, INCLUDING THEIR MOLECULAR BASIS AND CLINICAL, PATHOLOGICAL, AND BIOCHEMICAL FEATURES

Disease	PMIM #	Gene Associated	Cytogenetic Location	Gene Product	Function	Inheritance	Liver Phenotype	Pathological Features	Mitochondrial Features	Biochemical Features	Additional Features
Transient infantile liver failure	613070	TRMU	22q13.31	tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase	Mitochondrial translation	AR	Liver failure: acute, transient	Liver: fibrosis, macrovesicular steatosis	Deficiency of complex IV	Lactic acidosis	Disease resolution in patients surviving infantile liver failure event
mtDNA depletion syndrome 3: hepatocerebral type	251880	DGUOK	2p13.1	Deoxyguanosine kinase	mtDNA maintenance	AR	Liver failure: progressive, hepatocellular carcinoma	Muscle: normal Liver: variable	mtDNA depletion, variable deficiency of complexes I, III, and IV	Lactic acidosis, elevated transferrin saturation and ferritin, elevated alpha-fetoprotein	Cardiomyopathy Hypotonia, ophthalmoplegia, nystagmus May also present as noncirrhotic portal hypertension (PMIM # 617068)
mtDNA depletion syndrome 4A: Alpers type	203700	POLG	15q26.1	DNA polymerase gamma	mtDNA maintenance	AR	Liver failure: early, progressive	Brain: gray matter neuronal loss Liver: reactive astrocytosis, cirrhosis	mtDNA depletion, variable deficiency of complexes I, III, and IV	3-Methylglutaconic aciduria, elevated CSF protein	Epilepsy, psychomotor impairment, migraine headaches, cortical blindness
mtDNA depletion syndrome 4B: MNGIE type	174763	POLG	15q26.1	DNA polymerase gamma	mtDNA maintenance	AR	Liver failure: early, progressive	Muscle: ragged red fibers, cytochrome *c* oxidase negative fibers	mtDNA depletion, variable deficiency of complexes I, III, and IV		Gastrointestinal manifestations: dysmotility, pseudoobstruction, malabsorption; peripheral neuropathy, ophthalmoplegia, weakness
mtDNA depletion syndrome 6: hepatocerebral type (also: Navajo neurohepatopathy)	256810	MPV17	2p23.3	Mitochondrial inner membrane protein MPV17	mtDNA maintenance	AR	Liver failure: progressive; cholestatic liver disease	Liver: fibrosis Liver: steatosis, cirrhosis	mtDNA depletion, variable deficiency of complexes I, III, and IV	Lactic acidosis, hypoglycemia	Neuropathy, psychomotor impairment or regression, growth failure

TABLE 1. CONTINUED

Disease	PMIM #	Gene Associated	Cytogenetic Location	Gene Product	Function	Inheritance	Liver Phenotype	Pathological Features	Mitochondrial Features	Biochemical Features	Additional Features
Combined oxidative phosphorylation deficiency 1	609060	GFM1	3q25.32	Mitochondrial elongation factor G1	Mitochondrial translation	AR	Liver failure	Liver: necrosis, severe mitochondrial deficiency	Variable deficiency of complexes I, III, and IV		Growth failure, microcephaly, structural brain anomalies, encephalopathy, cardiomyopathy, early death
Combined oxidative phosphorylation deficiency 2	610498	MRPS16	10q22.2	Mitochondrial ribosomal protein S16	Mitochondrial transcription	AR	Liver failure		Variable deficiency of complexes I, III, and IV	Lactic acidosis	Congenital brain anomalies, hypotonia, early death
Combined oxidative phosphorylation deficiency 3	610505	TSFM	12q14.1	Mitochondrial translation elongation factor Ts	Mitochondrial translation	AR	Liver failure	Muscle: ragged red fibers, cytochrome *c* oxidase negative fibers Heart: lipid deposition, fibrosis	Variable deficiency of complexes I, III, and IV		Hypotonia, rhabdomyolysis, cardiomyopathy, Leigh syndrome, optic neuropathy
Combined oxidative phosphorylation deficiency 4	610678	TUFM	16p11.2	Mitochondrial translation elongation factor Tu	Mitochondrial translation	AR	Liver failure		Variable deficiency of complexes I, III, and IV	Lactic acidosis, hyperammonemia	Brain imaging abnormalities (leukoencephalopathy), hypotonia
mtDNA depletion syndrome 8B: MNGIE type	612075	RRM2B	8q22.3	Ribonucleotide reductase subunit M2B	Mitochondrial transcription	AR or AD	Liver failure: rapidly progressive	Muscle: cytochrome *c* oxidase negative fibers, lipid deposition	mtDNA depletion, variable deficiency of complexes I, III, and IV	Lactic acidosis, amino aciduria, elevated creatine kinase	Growth failure, weakness, hypotonia, epilepsy
mtDNA depletion syndrome 7: hepatocerebral type	271245	TWNK	10q24.13	Twinkle mtDNA helicase	mtDNA maintenance	AR	Liver failure: progressive	Liver: variable, including cirrhosis, steatosis, and hemosiderosis	mtDNA depletion, variable deficiency of complexes I, III, and IV	Anemia, electrolyte abnormalities	Encephalopathy, movement disorders, hypotonia, renal impairment/tubulopathy
mtDNA depletion syndrome 9: encephalomyopathic type with MMA	245400	SUCLG1	2p11.2	Succinate-CoA ligase, alpha subunit	mtDNA maintenance	AR	Liver failure	Muscle: variable fiber size with atrophy, lipid accumulation, ragged red fibers, cytochrome *c* oxidase negative fibers	Abnormal cristae on electron microscopy, variable deficiency of complexes I, III, and IV	Lactic acidosis, methylmalonic aciduria, elevated C3 on newborn screening	Hypertrophic cardiomyopathy, cognitive impairment, dystonia, sensorineural hearing loss, epilepsy, early death

TABLE 1. CONTINUED

Disease	PMIM #	Gene Associated	Cytogenetic Location	Gene Product	Function	Inheritance	Liver Phenotype	Pathological Features	Mitochondrial Features	Biochemical Features	Additional Features
GRACILE syndrome or mitochondrial complex III deficiency: nuclear type 1	603358 or 12400	BCS1L	2q35	BCS1 homolog, ubiquinol-cytochrome *c* reductase complex chaperone	Oxidative phosphorylation	AR	Cholestatic liver disease, hepatitis	Hemosiderosis	Deficiency of complex III	Lactic acidosis	Growth failure, amino aciduria, iron overload, early death
Pearson marrow-pancreas syndrome	557000	Multiple	Contiguous mtDNA deletion syndrome		Spontaneous	Cholestatic liver disease, liver failure	Bone marrow: vacuolization	mtDNA depletion, variable deficiency of complexes I, III, and IV	3-Methylglutaconic aciduria	Sideroblastic anemia, pancytopenia, exocrine pancreatic dysfunction, endocrinopathies; can progress to Kearns-Sayre syndrome	
Mitochondrial complex IV deficiency: nuclear type 4	619048	SCO1	17p13.1	Synthesis of cytochrome *c* oxidase 1	Oxidative phosphorylation; copper homeostasis	AR	Cholestatic liver disease	Liver: lipid vacuoles, steatosis Muscle: lipid accumulation	Deficiency of complex IV	Ketoacidosis, lactic acidosis	Encephalopathy, cardiomyopathy
Combined oxidative phosphorylation deficiency 19	615595	LYRM4	6p25.1	LYR motif-containing protein 4	Iron homeostasis	AR	Cholestatic liver disease		Deficiency of complexes I, II, and III	Lactic acidosis	Severe in the neonatal period with potential for full recovery
3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	614739	SERAC1	6q25.3	Serine active site-containing protein 1	Phosphatidylglycerol remodeling	AR	Liver failure, cholestatic liver disease: infantile onset	Liver: steatosis, cirrhosis, fibrosis	Mild mtDNA depletion, variable deficiency of complexes I, III, and IV	3-Methylglutaconic aciduria, hyperammonemia	Dystonia, hypoacusis, hypotonia, poor feeding, short stature, myopathy
DLD deficiency	246900	DLD	7q31.1	DLD	Subunit for dehydrogenase enzymes	AR	Recurrent fulminant liver failure	Liver: Reye-like appearance, mild fibrosis and/or increased glycogen deposition	Variable deficiency of complexes I, III, and IV	Metabolic decompensation with urinary alpha-ketoacids, lactic acidosis, presence of alloisoleucine, elevated citrulline on newborn screen (variable)	Early-onset neurological involvement, hepatomegaly, myopathy

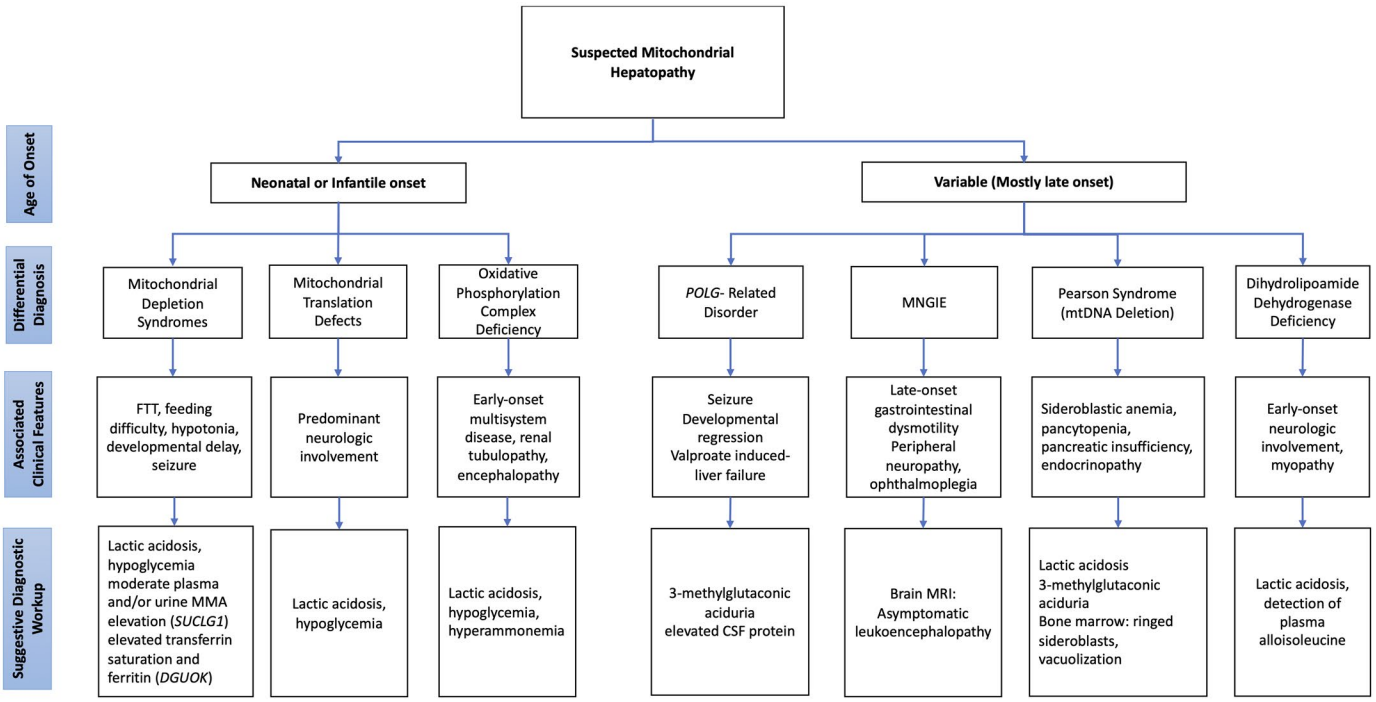

FIG 1 Diagnostic algorithm for mitochondrial hepatopathies.

Acquiring tissue samples enables functional mitochondrial testing. Electron transport enzymology is sensitive for *BCS1L* (complex III) and *SCO1* (complex IV) deficiency. BN-PAGE can suggest mitochondrial translation defects; mtDNA quantification is the diagnostic gold standard for MDS diagnosis. Functional testing is most sensitively performed on liver tissue. Because there is a high degree of phenotype overlap, whole-exome sequencing is often the most effective way to reach a definitive diagnosis. Analysis of mtDNA to rule out deletion is also warranted.

MANAGEMENT

Evidence-based management guidelines for mitochondrial hepatopathies are lacking, and curative treatments are unavailable. Supportive measures led by a multidisciplinary team are the mainstay of therapy. Early introduction of enteral feeding optimizes mitochondrial function and minimizes lactic acidosis. Feeding tube placement may be required to ensure adequate nutritional support for patients. Avoidance of fasting and/or frequent feedings can prevent hypoglycemia. Specific therapies are indicated for some diagnoses: branched-chain amino acid restriction and riboflavin supplementation for dihydrolipoamide dehydrogenase (DLD) deficiency, and cysteine supplementation for TRMU deficiency.[6]

Liver transplantation for mitochondrial hepatopathy is controversial. Good outcomes have been reported in patients with mild MPV17 and DGUOK without neurological involvement.[3,5] However, posttransplant disease worsening has been observed in patients with MDS with any neurological involvement, especially in POLG. Generally, liver transplant is not contraindicated, but risks and benefits should be carefully evaluated. Posttransplant management is challenging because some immunomodulators are mitotoxic. Hematopoietic stem cell transplant has resulted in clinical improvement in some patients with MNGIE.[8]

Mitochondrial dysfunction is associated with impaired redox homeostasis and glutathione depletion. *N*-acetylcysteine may ameliorate oxidative stress and is a potential therapy for mitochondrial hepatopathies.[6] Gene therapy has shown experimental success for several monogenic liver disorders. The liver is amenable to gene therapy: it is easily targeted by adeno-associated virus vectors and is a lifelong replicating tissue.[11] Therefore, it holds future promise as a therapeutic option for mitochondrial hepatopathies.

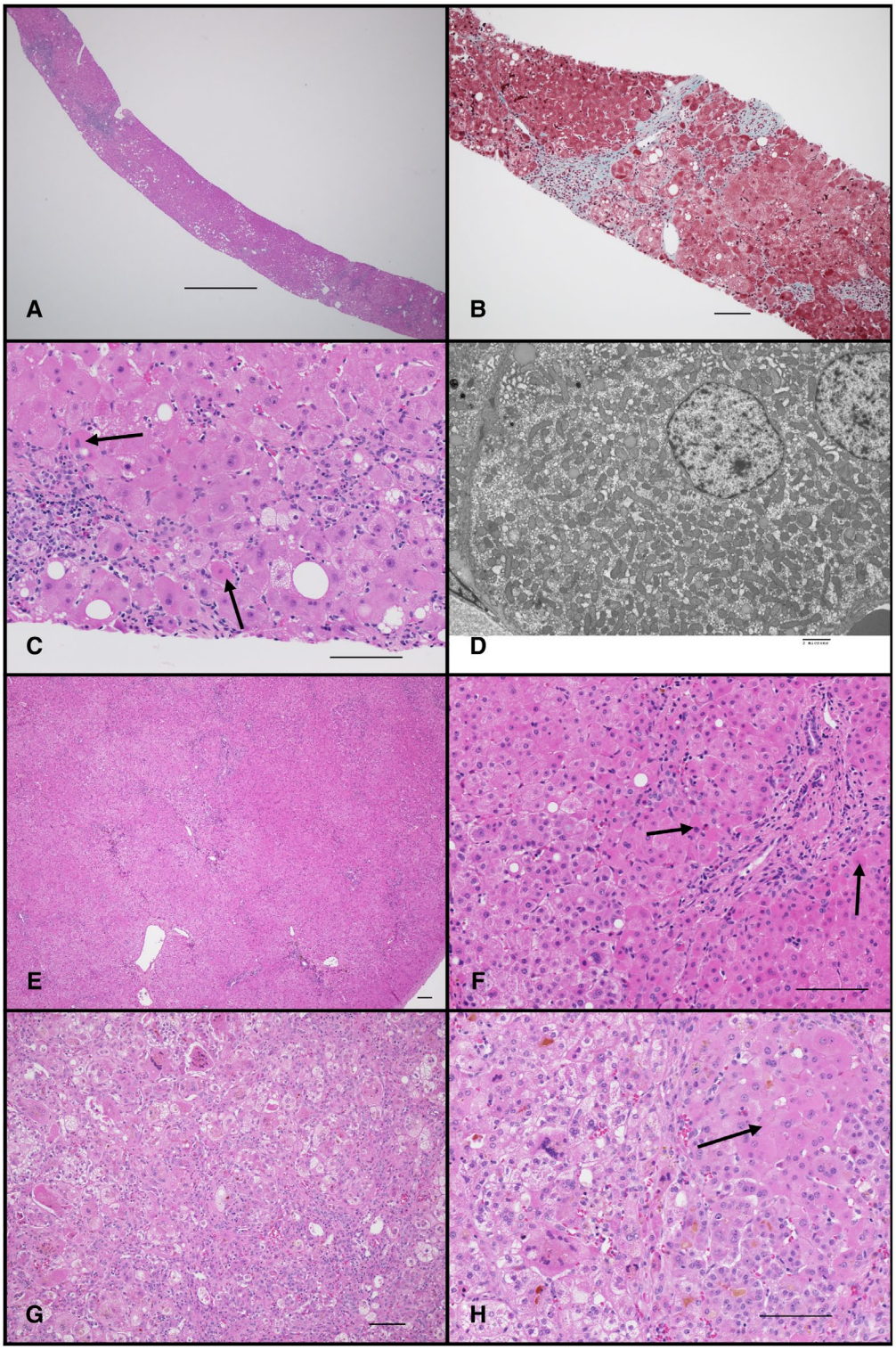

FIG 2 Pathological features of mitochondrial hepatopathy. (A-D) *MPV17* mutation in 18-year-old. (A) Liver needle biopsy showing patchy nonzonal steatosis and inflammation. (B) Gomori trichrome stain highlights patchy portal and sinusoidal fibrosis. (C) Higher-magnification image illustrating macrovesicular and microvesicular steatosis and oncocytic hepatocytes (arrows). (D) Electron micrograph of hepatocyte with proliferation of mitochondria lacking normal cristae. (E, F) *POLG* mutation in 9-month-old. Liver wedge biopsy with intact architecture, minimal macrovesicular steatosis, and numerous oncocytic hepatocytes (two highlighted by arrows). (G, H) *DGUOK* mutation, 7-week-old with acute liver failure. Liver explant with severe neonatal hepatitis pattern, characterized by giant cell transformation, hepatocellular and canalicular cholestasis, hepatocellular necrosis, and rare foci of oncocytic hepatocytes (arrow). Scale bars: 1000 μm (A); 100 μm (B, C, E-H); 2 μm (D).

CONCLUSIONS

Mitochondrial hepatopathies are an important cause of infantile/pediatric liver failure. They should be suspected in patients with neonatal-onset liver dysfunction, steatosis, fulminant or acute disease, or in individuals with neuromuscular or multiorgan involvement.

POSTTEST

1. What are clinical features that should increase suspicion for underlying mitochondrial hepatopathy?

Mitochondrial hepatopathy should be suspected in cases of neonatal-onset liver dysfunction, steatosis, fulminant, or acute disease, or in individuals with neuromuscular or multiorgan involvement.

2. How are mitochondrial hepatopathies diagnosed?

Diagnosis of mitochondrial hepatopathies is multifaceted and includes biochemical and genetic testing, pathological examination of liver tissue, and functional mitochondrial enzymology.

3. How are mitochondrial hepatopathies treated?

Treatment for mitochondrial hepatopathy is largely supportive. *N*-acetylcysteine may be helpful. Mitochondrial hepatopathy is not an absolute contraindication for consideration of transplantation.

CORRESPONDENCE

Rebecca D. Ganetzky, M.D., Division of Human Genetics, Children's Hospital of Philadelphia, ARC 1002G, 3615 Civic Center Blvd, Philadelphia, PA 19104. E-mail: ganetzkyr@email.chop.edu

REFERENCES

1) McKiernan P, Ball S, Santra S, et al. Incidence of primary mitochondrial disease in children younger than 2 years presenting with acute liver failure. J Pediatr Gastroenterol Nutr 2016;63:592-597.

2) Helbling D, Buchaklian A, Wang J, et al. Reduced mitochondrial DNA content and heterozygous nuclear gene mutations in patients with acute liver failure. J Pediatr Gastroenterol Nutr 2013;57:438-443.

3) Jankowska I, Czubkowski P, Rokicki D, et al. Acute liver failure due to DGUOK deficiency—is liver transplantation justified? Clin Res Hepatol Gastroenterol 2021;45:101408.

4) Visapää I, Fellman V, Vesa J, et al. GRACILE syndrome, a lethal metabolic disorder with iron overload, is caused by a point mutation in BCS1L. Am J Hum Genet 2002;71:863-876.

5) El-Hattab AW, Li F, Schmitt E, et al. MPV17-associated hepatocerebral mitochondrial DNA depletion syndrome: new patients and novel mutations. Mol Genet Metab 2010;99:300-308.

6) Murali CN, Soler-Alfonso C, Loomes KM, et al. TRMU deficiency: a broad clinical spectrum responsive to cysteine supplementation. Mol Genet Metab 2021;132:146-153.

7) Stumpf JD, Saneto RP, Copeland WC. Clinical and molecular features of POLG-related mitochondrial disease. Cold Spring Harb Perspect Biol 2013;5:a011395.

8) Filosto M, Cotti Piccinelli S, Caria F, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE-MTDPS1). J Clin Med 2018;7:389.

9) Wild KT, Goldstein AC, Muraresku C, et al. Broadening the phenotypic spectrum of Pearson syndrome: five new cases and a review of the literature. Am J Med Genet A 2020;182:365-373.

10) Molleston JP, Sokol RJ, Karnsakul W, et al. Evaluation of the child with suspected mitochondrial liver disease. J Pediatr Gastroenterol Nutr 2013;57:269-276.

11) Moscoso CG, Steer CJ. The evolution of gene therapy in the treatment of metabolic liver diseases. Genes (Basel) 2020;11:915.