Navajo Neurohepatopathy : A Case Report and Literature Review Emphasizing Clinicopathologic Diagnosis

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Abstract

Navajo Neurohepatopathy (NNH) is a rare hepatocerebral mitochondrial DNA (mtDNA) depletion syndrome (MDS) with nonspecific clinical or pathologic features aside from Navajo ancestry. Because of the rarity of NNH, diagnosis rests on close clinicopathologic correlation and appropriate tissue triage for quantitative mtDNA analysis. We present a new case of NNH in which the clinical presentation and H&E liver biopsy histology indicated the need for NNH workup. Quantitative analysis of mtDNA in liver tissue was significantly reduced, and mutational analysis of the MPV17 gene confirmed homozygosity for the NNH-associated missense mutation, R50Q. The patient is now one year post liver transplant and continues to have normal liver function tests but suffers multiple immunosuppression-associated co-morbidities. A comprehensive literature review is provided to assist in diagnosis and management of NNH. (Acta gastroenterol. belg., **2016**, 79, **463-469**).

Key words : hepatocerebral MDS, mitochondrial DNA depletion syndrome, navajo neurohepatopathy, MPV17 mutation, childhood liver failure, liver transplant.

Introduction

Navajo Neurohepatopathy (NNH) is a rare, autosomal recessive mitochondrial DNA (mtDNA) depletion syndrome (MDS) primarily affecting the liver and nervous system, both centrally and peripherally (1). NNH is caused by R50Q mutation of the nuclear MPV17 gene which encodes an inner mitochondrial membrane protein theorized to participate in maintenance of mtDNA, a requirement for normal cellular energy production (1,2). NNH, like other MPV17-related forms of hepatocerebral MDS, presents with liver failure in infancy or early childhood (3). A review by El-Hattab et al (4). in 2012 indicated that a total of only 31 molecularly confirmed cases of MPV17-related hepatocerebral MDS had been reported (7), of which were of Navajo ancestry (1,2,4-11). While there is currently no curative treatment for NNH, liver transplant can alleviate hepatic dysfunction in the short term but neurological symptoms invariably progress (3).

We report the clinical and pathological features of NNH in a patient recently diagnosed at the University of New Mexico Hospital. We also present a literature review of MDS with a focus on NNH in order to expand upon the clinicopathologic features that may help pathologists consider this unusual diagnosis in pediatric patients presenting with liver failure.

Case history

A small for gestational age but otherwise healthy baby boy was born at 39 weeks to two parents of Navajo Native American ancestry. The mother's prenatal course was unremarkable and the parents were non-consanguineous. Newborn screening initially indicated an abnormal amino acid profile ; however repeat testing was normal. He was admitted at 11 days of age for poor weight gain which resolved within 1 day. His weight gain was acceptable until 6 months of age when he again dropped below the 5th percentile for both weight and height. He walked and had his first word by the age of 1 year, and had recovered in weight, but by the age of 18 months was again at less than the 5th percentile for weight. At the age of 2 years and 7 months he was hospitalized for failure to thrive and testing revealed an elevated alkaline phosphatase and aspartate aminotransferase (AST) ; low serum albumin ; normal alanine aminotransferase (ALT) and normal bilirubin, suggesting hepatic synthetic dysfunction (Table 1). Testing was negative for hepatitis A, B and C. In addition, iron studies, TSH, creatine kinase, cortisol level, alpha-1-antitrypsin level, anti-endomysial IgA, amylase, abdominal ultrasound and fecal lipids to assess malabsorption were normal (Table 2). He did have a low ceruloplasmin level which pediatric gastroenterology attributed to inadequate caloric intake (Table 2). His eye exam was negative for Kayser-Fleischer rings. The patient was discharged after 10 days with scheduled follow-up and was referred for a dysmorphology and genetics workup at the beginning of his third year. This workup revealed no dysmorphic features to suggest a syndromic diagnosis, and karyotype and metabolic studies were deemed unnecessary given the second normal newborn screen, negative family history for inborn errors of metabolism or liver disease, and two

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Table 1. — **Laboratory values beginning at the time of hospitalization for failure to thrive at age 2 year, 7 months through liver transplant at age 3 years, 8 months and ending 3 days prior to death.**

Age:	2 yr, 7 mo	2 yr, 9.5 mo	2 yr, 11 mo	3 yr, 2 mo	3 yr, 6 mo	4 yr, 2 mo	5 yr, 1.5 mo	Normal Range
Clinical state:	**Hosp. for FTT***	**Checkup**	**Checkup**	**Hosp. for Ascites**	**2 mo < liver transplant**	**6 mo > liver transplant**	**3 days < death**	
Weight (kg)	9.94	9.81	10.2	12.7, 10.4*	12.1	12.8	16.2	
Percentile for age	<1%	<1%	1%	9.4%, <1%*	1%	1%	12%	
Blood Chemistry								
pH, venous blood							7.26 (L)	7.32-7.43
Lactate (mmol/L)				2.5 (H)				1.0 - 2.4
Sodium (mmol/L)	139	138	138	135 (L)	137	141	141	136 - 145
Potassium (mmol/L)	2.8 (L)	4	3.7	3.5	4.3	4.7	5.1 (H)	3.5 - 5.1
Chloride (mmol/L)	105	108 (H)	106	105	105	115 (H)	96 (L)	98 - 107
Calcium (mg/dL)	8.2 (L)			7.8 (L)	8.2 (L)	8.4 (L)	8.7	8.6 - 10.2
CO_2 (mEq/L)	15 (L)	19 (L)	19 (L)	16 (L)	21 (L)	20 (L)	42 (CH)	22 - 29
Anion Gap (mmol/L)	19.0 (H)	11	13	14	11	6 (L)	<6 (L)	8.0 -16
Glucose (mg/dL)	101		80	43 (L)	69 (L)	78	98	70 - 115
BUN (mg/dL)	13	12	7	7	4 (L)	6 (L)	33 (H)	7.0 - 18.0
Creatinine (mg/dL)	0.3 (L)	0.4 (L)	0.5 (L)	0.3 (L)	0.25 (N: 0.19-0.72)*	0.35 (N: 0.19-0.72)*	0.66 (N: 0.19-0.72)*	0.7 - 1.2
Liver Function Tests								
AST (IU/L)	129 (H)	177 (H)	144 (H)	335 (H)	122 (H)	31	26	0 – 40
ALT (IU/L)	58 (H)	61 (H)	52 (H)	71 (H)	24	40	16	0 – 41
GGT (IU/L)				253 (H)		13	11	3.0-22
Alk Phos (IU/L)	570 (H)	544 (H)	561 (H)	581 (H)	308 (N: 74-359)*	215 (N: 74-359)*	290 (N: 74-359)*	40 - 129
Albumin (g/dL)	3.0 (L)	2.8 (L)	2.7 (L)	2.0 (L)	2.3 (L)	2.5 (L)	2.8 (L)	3.4 – 5.0
Prealbumin (mg/dL)				<7 (L)				14-30
Protein, total (g/dL)				5.5	6.4	6	8	5.4-8.3
Biliburin, T (mg/dL)	1.3 (H)	1.2	1.43 (H)	3.1 (H)	4.4 (H)	<0.1 (L)	0.4	0 - 1.2
Bilirubin, I (mg/dL)				0.8	1.7 (H)	UAC*	UAC*	0.2 - 1.0
Bilirubin, D (mg/dL)				1.9 (H)	2.7 (H)	<0.1 (L)	<0.1 (L)	0.1 - 0.4
PT (s)	15.6 (H)		16.6 (H)	21.7 (H)	24.5 (H)	16.1 (H)	15.5 (H) (4y6mo)	12.2 - 14.3
INR	1.52 (H)		1.34 (H)	2.0 (H)	2.29 (H)	1.32 (H)	1.26 (H) (4y6mo)	0.8 - 1.2

Table 1 continued. — **Laboratory values beginning at the time of hospitalization for failure to thrive at age 2 year, 7 months through liver transplant at age 3 years, 8 months and ending 3 days prior to death.**

PTT (s)		36.4	42 (H)	42 (H)	41 (H)	33 (4y6mo)	26.0 – 36.9
Fibrinogen (mg/dL)			83 (L)				170-470

Abrevations: FTT = failure to thrive; UAC = unable to calculate; Clinical scenario row, < = before and > = after; elevated values are indicated by (H), low values are indicated by (L), and (C) designates critical values. The patient's weight at age 3 years, 2 months (while hospitalized for ascites) includes two values: prior to (12.7 kg, 9.4%) and after (10.4, 1%) treatment. Because normal range values change with age for many laboratory indices, including creatinine and alkaline phosphatase, the normal ranges for older age are given in parentheses when these differ from the values listed in the "Normal Range" column. For lab values received close to but not at the exact age specified by the column, the age of the patient at the time of the test is given in parentheses.

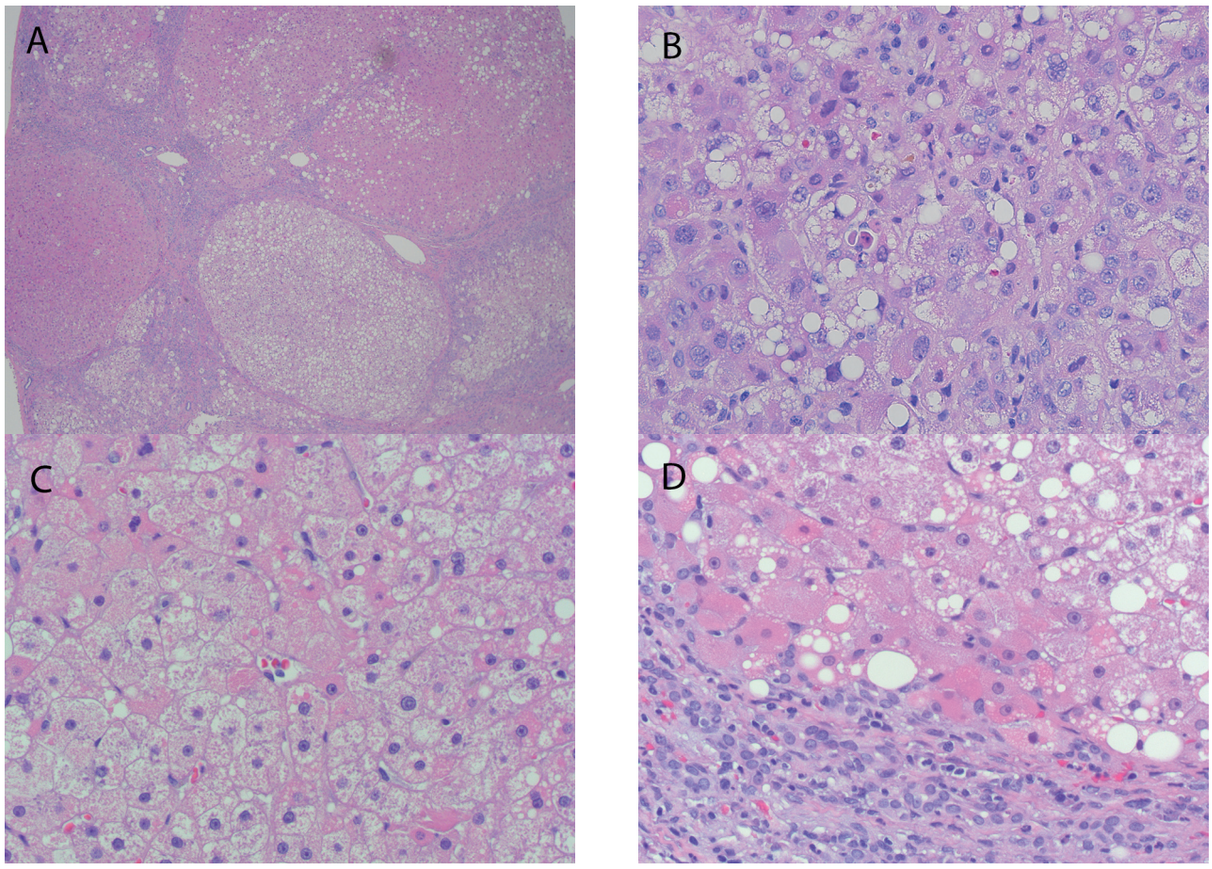

Fig. 1. — The liver biopsy showed a cirrhotic liver with diffuse steatosis (A) (H&E, x40). Higher power revealed predominantly macrovesicular steatosis with a few foci of microvesicular fat accumulation, as well as canalicular cholestasis and acidophil bodies (B) (H&E, x400). Few hepatocytes harbored large pink globules representing megamitochondria (C) (H&E, x 400). Scattered red granular hepatocytes were also present (D) (H&E, x400).

healthy older siblings. Clinical planning at that time included nutritional review to determine the patient's intake and need for dietary supplementation, as well as continued follow-up with pediatric gastroenterology for abnormal liver function tests and weight gain.

At the age of 3 years and 2 months, the child was hospitalized following a week of non-painful, acute abdominal swelling, dilated paraumbilical veins, and bright green stools. He was transferred to the University of New Mexico Hospital for additional workup which revealed severe liver dysfunction including coagulopathy (elevated PT, PTT and INR) ; elevated AST, ALT, alkaline phosphatase, and GGT ; low carbon dioxide, hypoalbuminemia, hypoglycemia, and low fibrinogen (Table 1). Additional testing for alpha-1-antitrypsin deficiency, inborn errors of metabolism, malabsorption, Wilson's disease, celiac disease, and pancreatic dysfunction yielded no definitive diagnosis (Table 2).

An abdominal ultrasound revealed a nodular, echogenic liver consistent with cirrhosis, and thus a liver biopsy was performed for histopathologic analysis and mtDNA depletion studies (the latter due to the patient's Navajo ethnicity).

Results

Histopathologic Findings

Histological examination demonstrated a fatty, cirrhotic liver with hepatocanalicular cholestasis, readily identifiable acidophil bodies, hepatocytes containing megamitochondria, and scattered red granular hepatocytes (Figure 1). The pattern of steatosis was predominantly macrovesicular but foci of microvesicular steatosis were also present. Scattered ballooned hepatocytes indicated an element of mild steatohepatitis. The fatty changes were not diffuse but were variably present throughout the regenerative nodules (Figure 1A) while some nodules lacked significant fat accumulation. Moderate chronic inflammation (consisting of lymphocytes and rare plasma cells) was identified primarily within bridging fibrous septae as is typically seen in cirrhotic livers from any cause. A septal ductular reaction with associated neutrophils was also evident, though native bile ducts were not inflamed or otherwise damaged.

Ancillary Testing

Despite normal ceruloplasmin levels and the child's age falling short of that typically seen in Wilson's disease, this remained on the differential due to both histology (cholestatic steatohepatitis) and the clinical picture of liver failure. Accordingly, tissue was sent for quantitative copper analysis and revealed a mildly elevated hepatic copper concentration (99 μg/g ; normal range 15-55 μg/g), which was below the level (250 μg/g) commonly observed in untreated Wilson's disease. Additional tissue was flash frozen and sent for quantitative mtDNA content analysis to Baylor College of Medicine, Medical Genetics Laboratory in Houston, TX. This revealed a mtDNA content of 12% the mean value of age and tissue matched controls, and was therefore compatible with MDS. Genetic counseling was subsequently recommended as was germline MPV17 mutation testing given the child's Navajo ancestry. As suspected, the homozygous missense mutation, R50Q, almost exclusively seen in Navajo populations (3,4), was identified on a sample of whole blood analyzed by Prevention Genetics, Marshfield, Wisconsin.

Clinical Course

At the age of 3 years and 8 months, orthotopic liver transplantation was performed at an outside institution. The child did well initially and was transferred home on chronic immunosuppressive therapy. His extended post-transplant recovery, however, was hampered by hospitalizations for EBV-associated respiratory failure, recurrent Clostridium difficile (C. difficile) colitis, hematochezia, septic shock with multi-organ failure, severe metabolic acidosis, stage IV sacral decubitus ulcer and C. difficile sacral osteomyelitis. Liver enzymes were closely monitored for signs of liver rejection (Table 1) and the patient's Tacrolimus levels were monitored for toxicity. A significant elevation in the patient's transaminases, GGT and alkaline phosphatase was observed at 1 year and 2 months post-transplant in the setting of sub-therapeutic immunosuppression while being treated for Tacrolimus-associated acute kidney injury and C. difficile colitis. Concerns for liver rejection were lessened, however, as these levels normalized with re-achievement of therapeutic immunosuppression. The combination of shock-associated renal injury and tacrolimus-associated renal toxicity resulted in severe kidney injury necessitating hemodialysis, continuous renal replacement therapy, chronic fluid restriction, and twice daily Lasix. Even with these treatments, the patient

Table 2. — **Additional laboratory testing.**

Laboratory Parameter	Age 2 years, 7 months (hospitalized for FTT)	Age: 3 years, 2 months (hospitalized for ascites)	Normal Range
Serum alpha fetoprotein (AFP) (ng/mL)		12,384 (H)	0-15
Plasma free fatty acids (mmol/L)		1.73 (H)	0.50 - 0.90
Plasma ammonia (µmol/L)		47	<51
Serum amino acids (mmol/L)		Normal	
Lipase (U/L)		58 (L)	59-269
Amylase (U/L)	Normal	37	<106
Alpha-1-antitrypsin (mg/dL)	Normal	97	90-200
Anti-endomysial IgA	Normal		
Ceruloplasmin (mg/dL)	16 (L)	18	17-46
Urine copper, 24 hr (mcg/24h)	9 (L)		15-60
Fecal lipids, 24 hr (g/24h)	2.2		<7

developed severe fluid overload and pericardial effusion by the age of 5. He also became blood transfusion dependent in the setting of anemia of chronic disease, and received red blood cell transfusions on average every other week and erythropoietin three times per week.

NNH-associated neuropathy manifested 1 year post-transplant as diffuse musculoskeletal pain and refusal to walk. The patient began treatment with gabapentin, daily physical therapy and a "mitochondrial cocktail" of B vitamins, coenzyme Q-10, and alpha lipoic acid. Other NNH-associated morbidities included metabolic (specifically lactic) acidosis secondary to mitochondrial depletion and respiratory acidosis secondary to poor respiratory effort (due to loss of respiratory muscle tone). The patient came to require oxygen, BiPAP and a gastric tube for near-complete replacement of oral feedings due to rapid tiring while eating. Ultimately, at the age of 5 years and 1.5 months, the child succumbed to respiratory failure, the result of progressive neuromuscular weakness due to NNH.

Discussion

History and Pathogenesis

The vast majority of adenosine triphosphate (ATP), the major source of cellular energy, is manufactured by an intricate series of protein complexes spanning the inner mitochondrial membrane, collectively termed the electron transport chain (ETC) (12). Some ETC proteins are encoded by mtDNA while others, including 70 respiratory chain subunits, are encoded by nuclear DNA.13,15 Several nuclear gene mutations have been associated with MDS (12,13). These mutations cause a quantitative decrease in mtDNA and insufficient synthesis of respiratory chain complexes I, III, and IV, leading to cellular ATP depletion (3,12-14). Because of their heavy reliance on ATP, the liver, brain, heart, and skeletal muscle are most susceptible to injury by this mechanism (12). While clinical presentations are variable, typically four phenotypes of MDS are recognized : myopathic, encephalomyopathic, hepatocerebral, and sometimes neurogastrointestinal (3,13). Tissue manifestations are associated with specific gene mutations. Thus far, the hepatocerebral form has been linked to mutations in the DGUOK,15 polymerase ɣ (1,16) MPV17 (2) and Twinkle helicase genes (12,17).

MPV17, a nuclear gene encoding an inner mitochondrial membrane protein, has recently been recognized as a causative mutation in hepatocerebral MDS (2,7). As of 2012, a review by El-Hattab et al.4 revealed that approximately 31 molecularly confirmed cases of MPV17-related hepatocerebral MDS had been reported (1-11). First described in 2006 (2), MPV17-related MDS has been attributed to several mutations of the MPV17 gene and has been identified in children of several ethnic backgrounds. These include but are not limited to 4 related children from southern Italy (2), 1 Caucasian child (10), 4 children in a 6-child sibship born to first-cousin Moroccan parents (2), 2 sisters born to Iraqi consanguineous parents (7), and 7 Navajo Native American children (4).

An entity termed Navajo neurohepatopathy (NNH) was first described in 1976 by Appenzeller et al. as an autosomal recessive disease affecting Navajo Native American children living in the southwestern United States (18). A major epidemiological survey of Navajo neuropathy by Singleton et al. (1990) showed the incidence of NNH to be over 5 times higher on the Western Navajo reservation than on the Eastern reservations (1 per 2, 632 as compared to 1 per 14, 286) (19). Other sources estimate the incidence of NNH within the Western Navajo reservations as 1 per 1, 600 live births (20). While several mutations of the MPV17 gene are known to cause MDS, those cases identified among Navajo children have been associated with the R50Q missense mutation which results in substitution of glutamine for arginine at position 50 (1,4,21). Although this specific mutation has been identified in children of other ethnic backgrounds, homozogosity for R50Q has only been observed in NNH.1 Nearly all children affected have liver disease, and three basic phenotypes have been described based on age at presentation (25). These include presentation before 6 months with jaundice, failure to thrive, and death by age 2 (infantile NNH) ; onset between 1 and 5 years with liver failure and death within 6 months (childhood NNH) ; and those with variable age onset of liver disease but with progressive neurological deterioration (classical NNH) (20,22). These phenotypes reflect variable disease expression, and provide a guideline for predicting disease progression.

Diagnostic Testing

Liver function tests in patients with NNH are relatively non-specific, though a notable increase in AST over ALT (similar to what is seen in alcoholic hepatitis) may indicate a mitochondrial hepatopathy. Lactic acidosis with an elevated molar ratio of lactate to pyruvate (>25 mol/mol) may also suggest mitochondrial hepatopathy (23,24). Liver biopsy reveals findings similar to other mitochondriopathies, most commonly macrovesicular and microvesicular steatosis, the latter of which can be quite extensive (25). Other common features include intralobular cholestasis, multinucleated hepatocytes, ballooning degeneration, scattered acidophil bodies, progressive portal fibrosis, and red granular hepatocytes containing an excess of mitochondria (10,25). Of all the histologic changes, steatosis remains the most consistent finding (9,15,23,25). These changes, while characteristic, are not specific. Histology by itself can only provide a differential diagnosis to include various metabolic disorders including Wilson's disease, tyrosinemia, galactosemia, hereditary fructose intolerance and glycogen storage disease, although some of these may have been previously excluded based on biochemical

testing. Due to the rarity of the disease, NNH is only suspected in infants and toddlers with the appropriate ethnic background who present with unexplained liver failure. When suspected, in addition to procuring liver tissue for light microscopy, flash frozen liver tissue (superior to muscle) should be sent for mtDNA quantitative analysis (12). This is usually performed using a real time quantitative PCR (RT-qPCR) assay and will consistently reveal a decrease in mtDNA content (<20% of age-matched controls) (4,10). Because of this depletion, electron transport chain activity assays performed on the same tissue will be reduced, most prominently in complex I or I + III (3,10). Once a mitochondrial depletion syndrome has been confirmed, genetic mutation analysis can be performed on whole blood. In our case, given the child's Navajo background, the MPV17 R50Q mutation was targeted to confirm the diagnosis.

Differential Diagnoses

MDS in general should be included in the differential diagnosis of infants and young children presenting with failure to thrive, hypoglycemia, lactic acidosis, elevated transaminases, evidence of unexplained liver failure, and, possibly, neurological impairment.4 NNH, in particular, should be suspected in Navajo Native American children in this same setting (4). The differential diagnosis includes more common metabolic derangements, fatty acid oxidation defects and urea cycle disorders, though these are often identified on newborn screenings. Infection and drug or toxin induced injury may be considered as these children present with hepatic injury demonstrating diffuse microvesicular steatosis. Entities including Reye syndrome, a transient post-viral hepatic mitochondriopathy often associated with aspirin use, and valproate toxicity, also resulting in mitochondrial toxicity, should be ruled out (26,27). A good clinical history to evaluate for recent viral infection and medications can help exclude these potential mimics. Wilson's disease also presents as unexplained hepatic dysfunction in children, albeit typically at an older age than those with NNH. Patients with Wilsons's disease often have non-specific pathological findings including steatosis, similar to MDS. To confound this issue, as evidenced by our case, hepatic copper content may be elevated in NNH, though it should not be elevated in the range characteristic of untreated Wilson's disease. Accordingly, quantitative copper analysis of liver tissue is helpful in excluding Wilson's disease though one must consider the degree of elevation when interpreting the result.

Treatment

There is currently no definitive evidence for the benefit of medical therapies in hepatocerebral MDS (12,28). In patients with liver failure, liver transplantation is currently the only treatment option, as few children survive without it (3). A multidisciplinary approach should be used and include specialists from hepatology, neurology, medical genetics, child development and nutrition. When acute liver failure occurs in neonates, therapy should include prevention of hypoglycemia as well as treatment of acidosis and hyperammonemia (13). In children with chronic liver disease, therapy relies on formulas enriched with medium-chain triglycerides, a diet with 30%-40% of energy as fat, hypoglycemia prevention, and fat-soluble vitamin supplementation.13 While several pharmacological therapies have been studied, there is little or no evidence to support their utility in treating most cases of MDS (28). There is, however, support for specific treatments for related diseases, including coenzyme Q deficiency and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (29). Future studies may evaluate the use of novel agents on defined clinical endpoints (e.g., survival and age at transplant) among populations with a specific gene mutation, such as that observed in NNH (13,28). Such a study would be difficult, however, based on extremely low disease incidence. Pfeffer et al. (2013) stress the importance of identifying disease biomarkers that correlate with clinically relevant endpoints, multidisciplinary input to identify new agents and mechanisms of therapy, and the importance of high-quality research using multicenter randomized control trials and disease registries to identify adequate patient numbers for study (30). Such collaborations as the North American Mitochondrial Disease Consortium, The Children's Mitochondrial Disease Network, and The German Network for Mitochondrial Disorders are pivotal to developing and improving study designs (30).

Promising opportunities for mitochondrial disorder treatment include genetic therapy, enzyme replacement therapy, small molecule therapy, bypass of electron transport complexes, and nutritional therapies (30). Small molecules, in particular, seem to be promising with the potential to selectively target the inner mitochondrial membrane and allow mitochondrial function to proceed (31). Genetic counseling is essential and should include evaluation of family members, particularly siblings, for targeted gene sequencing to determine carrier status (4). Family planning is also possible through pre-implantation genetic diagnosis (PGD) and prenatal genetic testing (4).

Conclusion

NNH is a rare form of hepatocerebral MDS seen in infants and young children of Navajo ancestry. It is caused by a mutation in the MPV17 gene and inherited in an autosomal recessive fashion. Histology typically reveals cholestatic steatosis/steatohepatitis which is characteristic of MDS in general but is not specific. Accordingly, the diagnosis relies on close multidisciplinary communication between clinicians and pathologists. Clinical suspicion is especially important so that pathologists have the foresight and opportunity to triage tissue for mtDNA depletion studies. Unfortunately,

NNH is an untreatable disease. Even liver transplant can only be considered palliative, and comes at the cost of immunosuppression-related morbidities. As more cases are studied and new therapies are developed, we can only hope that future treatments will improve the quantity and quality of life for afflicted children.

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