Navajo Neurohepatopathy: A Mitochondrial DNA Depletion Syndrome?

Tuan H. Vu,[1] Kurenai Tanji,[2] Stephen A. Holve,[3] Eduardo Bonilla,[1] Ronald J. Sokol,[4] Russell D. Snyder,[5] Stephany Fiore,[6] Gail H. Deutsch,[7] Salvatore DiMauro,[1] and Darryl De Vivo[7]

Navajo neurohepatopathy (NNH) is an autosomal recessive disease of full-blooded Navajo children living in the Navajo Reservation of southwestern United States. Clinical features of NNH include peripheral and central nervous system involvement, acral mutilation, corneal scarring or ulceration, liver failure, and metabolic and immunologic derangement. The cause of NNH is unknown, but the clinical features of NNH are similar to those of patients with mitochondrial DNA (mtDNA) depletion. Therefore, we studied mtDNA concentration in the liver from 2 patients with NNH. Using histochemical, biochemical, and molecular techniques, we found evidence of mtDNA depletion, and we propose that the primary defect in NNH is in the nuclear regulation of mtDNA copy number. (HEPATOLOGY 2001;34:116-120.)

First described by Appenzeller et al.[1] in 1976, Navajo neuropathy or neurohepatopathy (NNH) is an autosomal recessive disease affecting full-blooded Navajo children living in southwestern United States. The incidence of NNH is estimated at 1 per 1,600 live births in the western part of the Navajo Reservation, where most of the cases have been reported.[2] Affected children develop a severe progressive sensorimotor peripheral neuropathy with corneal ulceration and acral mutilation.[3] Many NNH patients also have episodes of Reye-like syndrome with elevated liver enzymes, and some have abnormal cerebral and cerebellar white matter signals on head computed tomography. Nerve biopsy results show an almost complete absence of large- and small-caliber myelinated fibers, with degeneration and regeneration of unmyelinated fibers.[1] Mean age at onset is 13 months, and most patients die during the first decade of life. Definite NNH is diagnosed when 4 of the following 6 criteria (or 3 plus a positive family history of NNH) are present: (1) sensory neuropathy; (2) motor neuropathy; (3) corneal anesthesia, ulcers, or scarring; (4) liver disease; (5) documented metabolic or immunologic derangement; and (6) central nervous system demyelination.[2,3] Although clinical features often overlap, patients with NNH can be divided into 3 groups: *classical NNH*, in which progressive neurologic disease is the main feature, although hepatopathy may occur in infancy; *infantile NNH*, in which jaundice and failure to thrive in infancy are followed by liver failure and death within the first 2 years of life; and *childhood NNH*, in which hepatopathy occurs acutely between the ages of 1 and 5 years, rapidly progressing to liver failure and death within months.[2] Different forms of NNH may be seen within a single family. There is no effective treatment. Liver transplantation was performed in a small number of patients; however, some of them later developed neurologic symptoms (Holve, unpublished observation). Because of the coexistence of neuropathy and hepatopathy in these patients and because the cause of death is related to liver failure, Holve et al.[2] have proposed that the syndrome be called "Navajo neurohepatopathy."

Because some clinical features of NNH (*e.g.,* hepatopathy and liver failure in young children, autosomal recessive inheritance, and nervous system involvement) are similar to the mitochondrial DNA (mtDNA) depletion syndrome (MDS),[4] we studied the liver from 2 NNH patients. Our results suggest that the defect in NNH may be in the nuclear regulation of mtDNA copy number.

PATIENTS AND METHODS

Patients

Patient 1 (Infantile NNH). Patient 1 was born at term with a normal birth weight. At age 1 month, she was noted to be malnourished, with no weight gain since birth. She had elevated bilirubin (total, 15.6 mg/dL; direct, 2.4 mg/dL), alkaline phosphatase (447 IU/L), aspartate aminotransferase (160 IU/L), alanine aminotransferase (166 IU/L), and creatine kinase (3,459 IU/L) levels. The following tests showed normal results or were negative: TORCH titers, α_1-antitrypsin, sweat test, hepatitis A and B serologies, DISIDA scan, liver ultrasound, and head computed tomography scan. Organic acid screen showed nonspecific abnormalities. She was admitted again at 4 months of age with failure to thrive (FTT). Length and head circumference were at the fifth percentile, and weight was significantly below the fifth percentile. Hepatomegaly was present. Biopsy results of the liver showed acute hepatocellular necrosis, cirrhosis, and mi-

cro- and macrovesicular fat in residual hepatocytes. Her prothrombin time and partial thromboplastin time were prolonged, vitamin E level was normal, and hepatitis C antibody was negative. A nerve biopsy showed no evidence of neuropathy. At 15 months of age, she had a markedly distended abdomen, ascites, decreased muscle mass, hypotonia, hyporeflexia, and delayed gross motor function, but no corneal ulceration. A nerve conduction study was normal, but brain magnetic resonance imaging showed diffuse white matter change consistent with demyelination. She underwent a liver transplantation at 16 months of age. At 21 months of age, she developed acute rejection and was treated successfully. However, she continued to have FTT. At 2.5 years of age, she developed acute pneumonia and expired despite maximum intervention. A limited autopsy showed acute necrotizing pneumonitis and acute adrenal hemorrhage (Waterhouse-Friederichsen syndrome; a full autopsy was not permitted due to cultural belief). Family history was significant for a second cousin who was similarly affected.

Patient 2 (Classical NNH). Patient 2 was born at term and was healthy until age 4 months, when she developed seizures associated with hypoglycemia. At 6 months of age, she had FTT. Hepatitis viral serologies, autoantibodies, α_1-antitrypsin activity, sweat test, ceruloplasmin, glycogen branching, and debranching enzyme activities were normal or negative. Liver enzymes were mildly increased. Percutaneous liver biopsy results at 20 and 30 months of age showed micronodular cirrhosis, mild steatosis, and intracellular glycogen accumulation, consistent with chronic active hepatitis. Subsequent electrodiagnostic study showed evidence of neuropathy, and brain magnetic resonance imaging showed white matter changes consistent with demyelination. She developed hepatocellular carcinoma at 11 years of age and underwent liver transplantation. She is alive at 16 years of age. She had an older brother who also had FTT, hypoglycemia, chronic liver failure, and died at 5 years of age from bleeding gastroesophageal varices.

Tissues

Liver tissue was obtained at transplantation from both NNH patients and stored at $-70°C$. Twenty-two control autopsy liver samples, from children ages 1 day to 2 years of age, were obtained from the Brain and Tissue Bank for Developmental Disorders at the University of Maryland (Baltimore, MD). The causes of death in this normal control group included sudden infant death syndrome (n = 13), accidental death (n = 9), and infection (excluding viral hepatitis; n = 4). The disease control group included 25 archival autopsy samples from patients 2 months to 18 years of age with various liver diseases. These diseases included cirrhosis caused by viral hepatitis (n = 3) and biliary atresia (n = 3), giant cell hepatitis (n = 4), neonatal iron storage disease (n = 3), tyrosinemia (n = 1), Alagille syndrome (n = 2), toxic injury (n = 3), glycogen storage (n = 2), Wilson's disease (n = 1), α-1-antitrypsin deficiency (n = 2), and unspecified autoimmune disease (n = 1). All liver samples were frozen in liquid nitrogen and stored at $-70°C$ or in liquid nitrogen until the time of study. Institutional Review Board approval for the use of autopsy and discarded tissues was obtained.

Quantitative Southern Blots

For quantitative Southern blots, 10 μg of total DNA was used. The procedure was as described previously.[4] Briefly, the DNA was digested with *Pvu*II (Boehringer-Mannheim, Indianapolis, IN), electrophoresed through a 0.8% agarose gel, and transferred to nitrocellulose membrane (Bio-Rad, Hercules, CA). The membranes were hybridized simultaneously with 2 probes. The mtDNA probe was an α-[32P]-labeled 15.7-kb-long template polymerase chain reaction fragment of the human mtDNA (nt 12,123 to nt 11,272). The other probe, also α-[32P] labeled, was 1.8 kb in length and specific for the nuclear 18S rDNA gene. The intensity of the hybridization to the second probe served as an internal control for the amount of total DNA loaded in each lane. Membranes containing DNA from patients and controls were hybridized on the same day using the same batch

of probes and exposed to the same experimental conditions. The intensity of the mtDNA and nuclear DNA signals was determined using a molecular imager system (Bio-Rad, Hercules, CA), and the ratio of the 2 signals was calculated for each sample. In addition, the origin of replication of the mtDNA light and heavy strand (O_L and O_H, respectively), the conserved sequence block region of the mtDNA, and the gene for human mitochondrial transcription factor A (h-mtTFA) were sequenced using standard methods. Deletions and rearrangements of mtDNA were excluded by polymerase chain reaction–based methods.[5]

Biochemistry and Histochemistry

Mitochondrial enzymes were studied as previously described.[6-9] We measured the activities of cytochrome *c* oxidase (COX, complex IV), succinate-cytochrome *c* reductase (complexes II and III), NADH-cytochrome *c* reductase (complexes I and III), NADH-dehydrogenase (complex I), succinate dehydrogenase (SDH, complex II), and citrate synthase (a matrix enzyme) in liver extracts.

RESULTS

Morphology and Histochemistry

Morphologically, the liver of patient 1 showed micro- and macrovesicular steatosis, ballooning degenerating hepatocytes, bile canalicular plugging, prominent portal and bridging fibrosis, regenerative nodules, and inflammation (Fig. 1A and B). COX histochemistry showed normal activity in only a few hepatocytes (Fig. 1C), whereas most hepatocytes were COX deficient, with normal to increased SDH activity (Fig. 1D). In the liver of patient 2, cirrhosis with micro- and macroregenerative nodules were present (not shown).

Biochemistry

The activity of COX (complex IV of the respiratory chain) was decreased in liver from both patients relative to normal controls (Table 1); the liver of patient 1 also had decreased succinate cytochrome c reductase (complexes II and III) activity. The activity of citrate synthase, an index of mitochondrial mass, was significantly increased in patient 1, suggesting mitochondrial proliferation. When the mitochondrial respiratory chain activities of this patient are referred to the activity of the nuclear encoded citrate synthase, then COX and succinate cytochrome *c* reductase activities are markedly decreased, and NADH cytochrome c reductase (complexes I and III) activity is also decreased. In patient 2, the activity of SDH (a nuclear-encoded enzyme) was decreased, but the activity of citrate synthase (also nuclear encoded) and the SDH histochemistry were normal. There was not sufficient tissue to confirm the SDH biochemical result or to determine the activities of other enzymes in patient 2.

DNA Analysis

There were no mutations in the O_H, O_L, conserved sequence block regions of the mtDNA, or in the h-mtTFA gene, and no detectable deletions or large-scale rearrangements of the mtDNA in the 2 patients. Quantitative Southern blot showed 89% and 82% depletion of mtDNA in patients 1 and 2, respectively, as compared with the average liver mtDNA content of 22 age-matched normal controls (Fig. 2). Relative to the disease controls as a group, patients 1 and 2 had 82% and 70% mtDNA depletion. The mtDNA content in the liver of NNH patients was similar to those with MDS (Fig. 3). The disease control samples also had less mtDNA than normal controls; however, 2 of 25 (8%) had more severe mtDNA depletion than
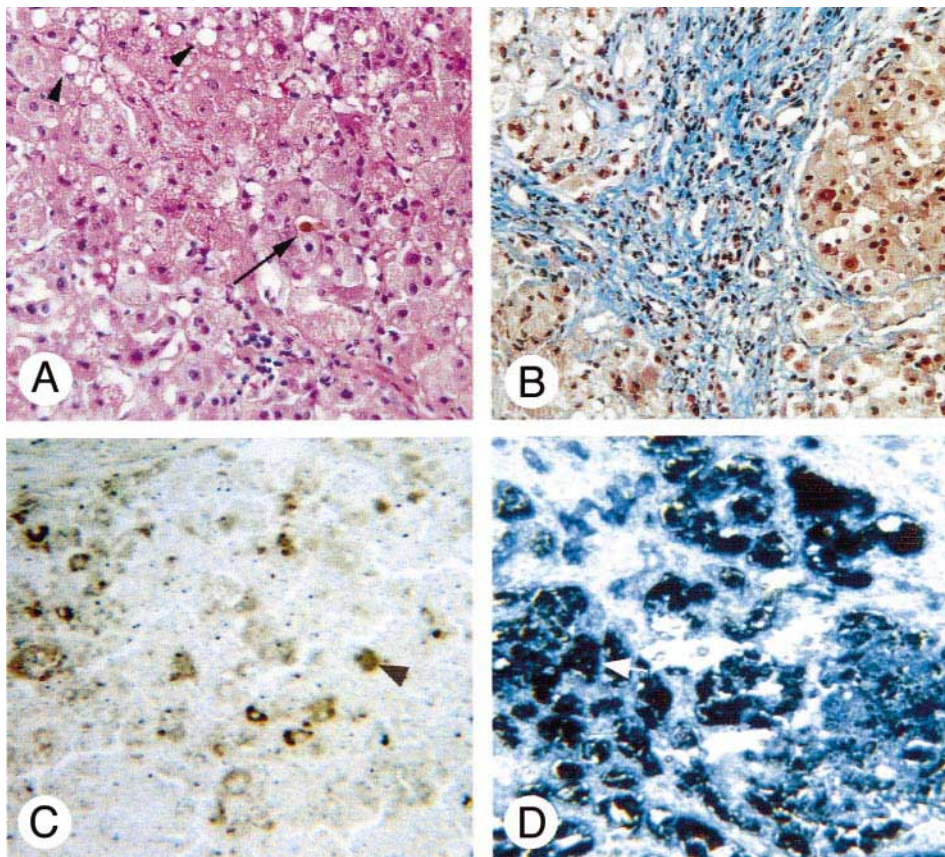
FIG 1. Morphologic and histochemical findings in the liver of a patient with infantile NNH (patient 1). (A) Hematoxylin and eosin stain shows cholestasis with ballooning degeneration of hepatocytes, including multinucleated forms. Mixed macro- and microvesicular steatosis (*arrowheads*) and bile canalicular plugging (*arrow*) are present. (B) The trichrome stain highlights the presence of portal and bridging fibrosis with regenerative nodules. A moderate degree of mixed inflammation is present within the portal tract. (C) COX staining shows normal activity in only a few hepatocytes (*arrow*), whereas most hepatocytes are COX deficient. (D) SDH shows normal to increased activity in most hepatocytes. (A and B, original magnification ×150; C and D, ×160.)

patients with NNH. These 2 patients, one with fulminant hepatitis A and another with iron storage disease, had 92% and 91% depletion of mtDNA, respectively.

DISCUSSION

The evidence for a mitochondrial etiology in NNH is compelling. A previous study reported laboratory abnormalities suggestive of mitochondrial dysfunction in a number of patients with NNH.[2] These abnormalities include elevated serum lactate levels and ultrastructural mitochondrial abnormalities (ringed cristae, swelling and loss of cristae, and pleomorphic mitochondrial contour). We also noted several common clinical features between patients with NNH and MDS: Hepatopathy and liver failure in young children, autosomal recessive inheritance, and nervous system involvement (white matter abnormalities and peripheral neuropathy).

Patients with MDS may have involvement of single or multiple tissues, including brain, liver, muscle, and kidney. Patients with the hepatopathic form of MDS are symptomatic in the first year of life and die within a few years after onset.[10,11]

Similarly, patients with infantile NNH present with hepatic symptoms before 6 months of age, those with the childhood form present between 1 and 5 years of age, and most die within a few years.[2] Infants with hepatopathy and mtDNA depletion often have persistent vomiting, FTT, hypotonia, and hypoglycemia. These symptoms are also commonly seen in children with NNH. In terms of laboratory findings, liver abnormalities in the hepatopathic form of MDS include steatosis, cholestasis, bile duct proliferation, fibrosis, collapse of liver architecture, decreased COX histochemical stain, and decreased activities of respiratory chain enzymes containing mtDNA-encoded subunits.[11-15] In all NNH patients studied,[2] histologic findings in liver are similar to those seen in patients with MDS. In particular, liver pathology in patient 1 was remarkably similar to that of a child with liver mtDNA depletion reported by Ducluzeau et al.[11] In this study, we also found focal COX deficiency by histochemistry in hepatocytes, with normal activity of SDH (an enzyme exclusively encoded by nuclear DNA). Accordingly, biochemistry also showed decreased COX activity relative to controls. Quantitative South-

TABLE 1. Mitochondrial Enzyme Biochemistry

Patient	Cytochrome c Oxidase*	Succinate Cytochrome c Reductase*	NADH Cytochrome c Reductase*	Citrate Synthase*	NADH Dehydrogenase*	SDH*
Patient 1	0.51	0.64	2.52	26.10	82.76	5.20
Patient 2	0.25	—	—	8.80	—	0.75
Controls	1.62 ± 0.51	1.80 ± 0.96	2.79 ± 1.00	6.59 ± 1.21	62.38 ± 22.7	4.72 ± 1.99

NOTE. Patients with NNH have decreased activity of several respiratory chain enzymes.
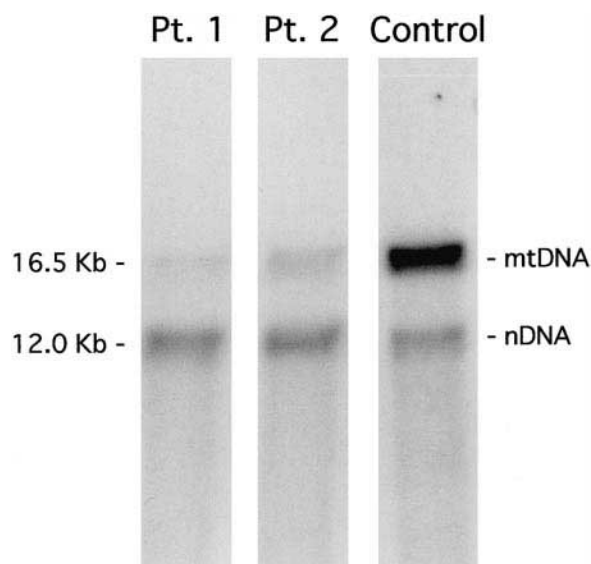
*mmol/min/g.

FIG. 2.   Autoradiogram of Southern blot of total DNA extracted from the liver of patients with NNH. The intensity of hybridization to the mtDNA probe (*top bands*) corresponds to the quantity of mtDNA present in each sample. The nuclear DNA signals (*bottom bands*) serve as an internal control for the amount of total DNA loaded in each lane. Compared with controls, both patients' mtDNA content in the liver was significantly decreased.

ern blot showed marked (>80%) depletion of mtDNA in the NNH patients' liver relative to age-matched normal controls. Of interest, there was less residual mtDNA in the liver of the more severely affected patient. Characteristically, children with mtDNA depletion have hyperCKemia,[16] which is also a feature of a few NNH patients (*e.g.,* patient 1 in this report). Together, these findings suggest that depletion of mtDNA plays a pathogenetic role in NNH.

Although there are significant clinical, morphologic, and biochemical similarities between MDS and NNH, we have considered the possibility that the mitochondrial defects in NNH may be secondary—that is, the consequence of other, as yet unidentified pathologic mechanisms. However, known causes of liver failure in young children, including amino and organic acidopathies, disorders of very long chain fatty acids, lysosomal diseases, disorders of cholesterol and bile acid synthesis, disorders of carbohydrate and glycoprotein synthesis, and heavy metal toxicity have all been excluded in NNH patients so studied.[2] Nevertheless, to determine whether mtDNA depletion might be a secondary phenomenon in hepatic diseases or a result of end-stage liver failure, we quantified liver mtDNA content in autopsy samples from several patients with known hepatopathies. We did find that liver mtDNA content in these patients was decreased relative to normal controls; however, most did not have the same degree of mtDNA depletion seen in patients with NNH. There were only 2 samples that had more severe depletion of mtDNA than NNH patients. These samples were from a 2-year-old patient who had fulminant hepatitis A infection and a 4-month-old patient with neonatal iron storage disease. However, histochemical studies distinguished these patients from those with MDS and NNH. In the patient with fulminant hepatitis A, the hepatocytes outside the areas of zonal necrosis retained COX activity. Similarly, despite extensive fibrosis and necrosis, the residual hepatocytes in the patient with iron storage disease were not histochemically COX deficient. COX deficiency is a

hallmark of mitochondrial dysfunction, and the lack of this feature in these 2 patients and its occurrence in the 2 Navajo patients suggest that mitochondrial involvement is a primary phenomenon in NNH.

Neuropathy is a feature of some patients with MDS[16] and the cardinal feature of classical NNH. In our patients with MDS, approximately 20% had white matter changes (unpublished observations). Central nervous system demyelination is common in children with NNH and is one of the diagnostic criteria. The pathogenesis of the neurologic abnormalities remains to be elucidated in both disorders, but the association of neurologic and hepatic manifestations is intriguing. The current population of 60,000 in the western portion of the Navajo Reservation descends from about 1,000 Navajo who fled from the United States military in the 1860s.[17,18] With subsequent geographic isolation, this population probably experienced a form of genetic drift known as the *founder effect*. Because of this effect, it is likely that the overlapping neurologic and hepatic diseases result from a single shared gene mutation rather than from multiple different genotypes. Abnormalities in tightly linked or contiguous genes might also explain the phenotypic variations in NNH.

The genetic defect in NNH is not known, but our findings of mtDNA depletion and mitochondrial dysfunction provide some important clues. Replication of mtDNA is dependent on several nuclear-encoded factors,[19,20] and a mutation in one of these factors may lead to mtDNA depletion. Lending support to this hypothesis are complementation studies fusing enucleated fibroblasts depleted of mtDNA with a human-derived cell line lacking mtDNA (ρ^0).[21] The resulting cytoplasmic hybrids had normal mtDNA levels and respiratory chain function, indicating that the nucleus of the ρ^0 cell line had complemented the nuclear defect(s) in the mtDNA-depleted cells. Among the nuclear factors, h-mtTFA has long been a suspect in mtDNA depletion. This 25-kd protein bends and unwinds mtDNA, priming and stabilizing it for transcription and replication.[19,22] Indeed, the mtTFA knock-out mouse has a dramatic depletion of mtDNA.[23] Mutations in the mtDNA at the origins of replication or in the conserved sequence block region theoretically may also impair mtDNA replication. However, we found neither mutations in the mtTFA gene nor
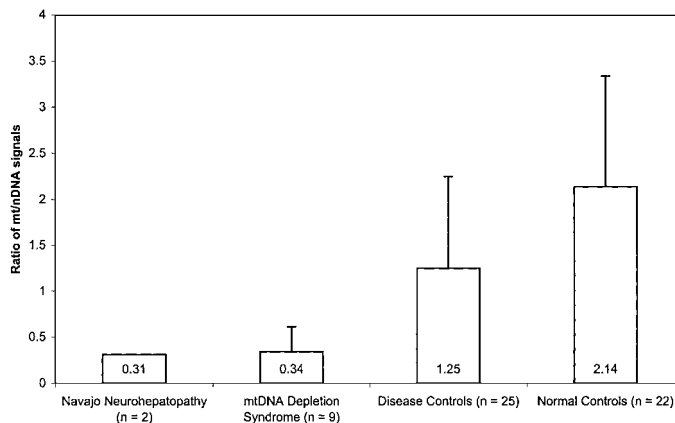

FIG. 3.   Mitochondrial DNA content in various liver diseases. The liver mtDNA content in patients with NNH, MDS, and other hepatopathies was decreased relative to that of the controls. Patients with MDS and NNH have the least amount of residual mtDNA. Numbers in columns correspond to the mitochondrial DNA/nuclear DNA ratio. Error bar = 1 standard deviation.

mtDNA mutations that can explain mtDNA depletion in our patients. Zhang and Arias[24] proposed another cause for NNH, based on their findings that expression of the multidrug-resistance 3 gene was decreased in the liver of patients with NNH. However, neurologic dysfunction and steatosis have not been reported in patients with inherited multidrug-resistance-3 deficiency.

In conclusion, NNH shares several clinical features with MDS. Furthermore, laboratory findings in NNH meet the proposed diagnostic criteria for the hepatic form of MDS,[10] including markedly reduced mtDNA content, COX deficiency on histochemical studies, respiratory chain defects, exclusion of other hepatopathies of infancy, and absence of drugs that may induce mtDNA depletion. Based on the available evidence, we propose that mtDNA depletion in NNH is a primary process caused by a defect in one of the nuclear DNA-encoded proteins involved in mtDNA replication. Confirmation of this hypothesis awaits the mapping and identification of the mutant gene, now underway.

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