CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 12-2011: A 9-Month-Old Boy with Acute Liver Failure

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PRESENTATION OF CASE

Dr. Jess L. Kaplan (Pediatrics): A 9-month-old boy was admitted to the hospital because of fever, diarrhea, and liver failure.

The patient had been well until 2 days before admission, when lethargy, irritability, rhinorrhea, intermittent vomiting, and nonbloody diarrhea developed, with decreased oral intake. The next day, the temperature reportedly increased to 38.1°C. He was seen in a health center associated with this hospital; the temperature was 37.6°C, and the physical examination was normal. Acetaminophen and a pediatric oral electrolyte solution were prescribed for presumed viral gastroenteritis, and he was sent home. The next day, symptoms worsened; in the evening, he was brought to the emergency department at this hospital.

The patient was born after a full-term gestation and was delivered vaginally; Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Results of routine newborn metabolic screening were normal. Hepatitis B vaccine was administered before discharge. One month before admission, he reportedly had a respiratory infection; 3 days before admission, he had fallen while taking his first steps and bruised his forehead. He had been well otherwise, with normal growth and development. His only medication was acetaminophen (120 mg every 4 to 6 hours as needed for fevers) for 1 day; childhood immunizations were reportedly up to date. He had no known allergies. He lived with his mother, who had had respiratory symptoms for 1 week and received azithromycin. He did not attend day care and did not have known travel or toxic exposures, including mushroom ingestion. His mother had had seizures in childhood.

On examination, he was listless, intermittently restless, and whimpering. The weight was 8.9 kg (25th to 50th percentile for age), the temperature 37.6°C, the blood pressure 95/46 mg Hg, and the pulse 133 beats per minute; the respiratory rate was 26 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The conjunctivae were pale and nonicteric. There was a bruise above the left eye. Bowel sounds were diminished, and the abdomen was soft, without tenderness or distention. The liver edge extended 4 to 5 cm below the costal margin. The

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remainder of the examination was normal. The levels of magnesium, C-reactive protein, amylase, lipase, iron, total iron-binding capacity, and lactate were normal; additional results are shown in Table 1. Urinalysis was normal, and screening of the urine for toxins was negative. A radiograph of the abdomen showed a nonspecific bowel-gas pattern, with no evidence of free air or bowel obstruction. Intravenous fluids were administered. Computed tomography (CT) of the brain, without contrast administration, was normal. Ultrasonography of the abdomen showed a slightly

Table 1. Laboratory Data.*

Variable	Reference Range, Adjusted for Age†	On Admission	1st Day	2nd Day	3rd Day
Hematocrit (%)	33.0–39.0	24.7	25.0 (manual)	21.8	20.0
Hemoglobin (g/dl)	10.5–13.5	9.2		8.1	7.4
White-cell count (per mm^3)	6000–17,500	19,300	8200	3900	4400
Differential count (%)					
Neutrophils	17–49	58	47	53	62
Band forms	0–10				4
Lymphocytes	67–77	39	48	44	31
Atypical lymphocytes	0	1			
Monocytes	4–11	1	4	3	1
Eosinophils	0–8		1		
Metamyelocytes	0	1			
Myelocytes	0				2
Platelet count (per mm^3)	150,000–400,000	400,000	231,000	285,000	280,000
Reticulocytes (%)	0.5–2.5		1.5		
Activated partial-thromboplastin time (sec)	21.0–33.0		26.7	32.0 (lipemic specimen)	36.3
Prothrombin time (sec)	10.3–13.2		18.1	16.8 (lipemic specimen)	18.7
International normalized ratio			1.7	1.6	1.8
D-Dimer (ng/ml)	<500		1628, repeated 2353		
Fibrinogen (mg/dl)	150–400		91		
Sodium (mmol/liter)	135–145	132	138	140	150
Potassium (mmol/liter)	3.4–4.8	5.7	2.8	3.0	3.3
Chloride (mmol/liter)	98–106	99	100	103	111
Carbon dioxide (mmol/liter)	22.0–27.0	18.7	24.2	24.3	24.1
Urea nitrogen (mg/dl)	5–20	40	25	26	30
Creatinine (mg/dl)	0.30–1.00	0.64	0.42	0.56	0.67
Glucose (mg/dl)	70–110	135	95	79	90
Bilirubin (mg/dl)					
Total	0.0–1.0	0.6	0.7	0.7	1.3
Direct	0.0–0.4	0.5	0.4	0.4	1.0
Protein (g/dl)					
Total	6.0–8.3	5.4	4.6	4.3	4.4
Albumin	3.3–5.0	4.1	3.6	3.4	3.3
Globulin	2.6–4.1	1.3	1.0	0.9	1.1

Table 1. (Continued.)

Variable	Reference Range, Adjusted for Age†	On Admission	1st Day	2nd Day	3rd Day
Alkaline phosphatase (U/liter)	15–350	297	277	249	293
Aspartate aminotransferase (U/liter)	9–80	1248	3528	3718	2133
Alanine aminotransferase (U/liter)	10–55	802	1664	1845	1920
Lactate dehydrogenase (U/liter)	110–210		2031		1875
Uric acid (mg/dl)	3.6–8.5		10.1		17.8
Phosphorus (mg/dl)	4.5–6.7		4.2	4.4	5.6
Calcium (mg/dl)	8.5–10.5		7.8	7.9	7.4
Creatine kinase isoenzymes (ng/ml)	0.0–6.9		18.5		
Creatine kinase (U/liter)	60–400		1407		
Ceruloplasmin (mg/dl)	27–50		20		
Ammonia (μmol/liter)	12–48		46	69	84
Ferritin (ng/ml)	30–300			1230	
Triglycerides (mg/dl)	40–150				340
Cortisol (μg/dl)	5–15 (between noon and 8 p.m.)				106.4 (4 p.m.)

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted and are for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

echogenic liver and pericholecystic fluid, with no evidence of intrahepatic or extrahepatic biliary-duct dilatation.

After sedation with midazolam, CT of the chest, abdomen, and pelvis with the administration of oral and intravenous contrast material showed a markedly enlarged liver with diffuse hypoattenuation consistent with fatty infiltration and pericholecystic fluid. The CT examination was otherwise normal.

The patient was admitted to the pediatric intensive care unit. A central line was placed in the femoral vein; cardiovascular and respiratory variables were monitored continuously; and oral intake was restricted. *N*-acetylcysteine and ceftriaxone were given; ranitidine and vitamin K were administered; lorazepam and morphine were given for agitation. The level of serum acetaminophen was less than 10.0 mg per liter (reference range, 10 to 25); none was detected in the urine. During the first 2 days, testing for serum heterophile antibodies, Epstein–Barr virus (EBV), and hepatitis A and C viruses was negative, as were tests for respiratory viruses (adenovirus, influenza A and B viruses, parainfluenza, and respiratory syncytial virus antigen) performed on a nasal specimen; testing for hepatitis B virus surface antibody was positive and surface antigen negative. Cultures of the blood, urine, and stool were sterile. Other laboratory-test results are shown in Table 1.

During the next 2 days, hypotension and hypoxemia developed, with systolic blood pressures of 60 to 70 mm Hg, diastolic pressures of 30 to 40 mm Hg, and an oxygen saturation of 88% while the patient was breathing ambient air; he became increasingly lethargic, with sluggish pupillary reactions. Oxygen by nasal cannula and normal saline boluses were administered; blood pressure returned to normal but then decreased; dopamine and norepinephrine were administered. Electrocardiography revealed a sinus rhythm of 153 beats per minute, with an incomplete right bundle-branch block and right ventricular hypertrophy; echocardiography was normal. CT of the head was normal.

Testing for syphilis, antibodies to toxoplasma and parvovirus B19, bartonella (immunoglobulins

IgG and IgM), varicella–zoster virus (IgG), and cytomegalovirus (CMV) antigen was negative; other results are shown in Table 1. On the third day, red cells were transfused; the hematocrit increased to 31.4%. The liver was 6 to 8 cm below the costal margin, extending to the umbilicus and firm to palpation. Additional test results were pending.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Marsha Kay Fearing: May we review the imaging studies?

Dr. Otto Rapalino: Abdominal ultrasonography performed on admission shows diffusely increased echogenicity in the liver parenchyma, which is compatible with fatty infiltration, without focal abnormalities, and a small amount of pericholecystic fluid (Fig. 1A). Abdominal CT performed for further evaluation of the liver showed fatty attenuation of the liver parenchyma, mild hepatomegaly, and a small amount of fluid surrounding the gallbladder (Fig. 1B).

Dr. Esther J. Israel: I am aware of the diagnosis in this case. The pediatric gastroenterology and hepatology service was asked to see this infant because of concern about acute liver failure. Criteria for acute liver failure in children include elevated aminotransferase levels for 8 weeks or less without preexisting liver disease, an international normalized ratio (INR) greater than 1.5 (or a prothrombin time ≥15 seconds) with encephalopathy, or an INR greater than 2.0 (or a prothrombin time >20 seconds) without encephalopathy.[1] On day 3, our patient had an INR of 1.8 with a prothrombin time of 18.7 seconds, and the INR increased to more than 2 by the fourth day, so he met the criteria for liver failure. It was difficult to ascertain whether he had encephalopathy, because he received midazolam and morphine for line placement on day 1, and he was stuporous without response to pain for at least 2 days thereafter.

Prophylactic antibiotics were initiated, and *N*-acetylcysteine was added, although its efficacy in non–acetaminophen-related acute liver failure in children is uncertain. The infant was also evaluated for possible liver transplantation. The cause of acute liver failure was then assessed.

The differential diagnosis of liver failure in this child includes the use of acetaminophen and other drugs, which are the most common identified cause of liver failure (16% of cases), metabolic disorders (10%), viruses (6%), and ischemia (4%).[2] The Pediatric Acute Liver Failure database shows that the cause of liver failure in children is not determined 49% of the time, although this varies according to the age of the child.[2] This patient was 9 months of age; in infants, metabolic disorders are more common than drug-related causes of liver failure. In one retrospective study of the literature,[3] metabolic causes were implicated in 42% of the infants with acute liver failure, and only 16% of the cases in that age group were of indeterminate cause. A recent evaluation of the Pediatric Acute Liver Failure database showed that children with acute liver failure of indeterminate cause had a less than complete evaluation for metabolic and autoimmune causes.[4]

Possible infectious causes in this case included herpes simplex virus, parvovirus, human herpesvirus 6, CMV, EBV, and hepatitis A, B, and C viruses; testing for these was negative, as were stool, urine, and blood cultures. Furthermore, most patients with liver failure due to primary hepatic infections present with hyperbilirubinemia and jaundice, whereas our patient had a normal bilirubin level.

Acute liver failure may be the initial manifestation of autoimmune hepatitis, although these disorders more often present as a chronic illness. An assessment should be done for antinuclear and anti–smooth-muscle antibodies for type 1 autoimmune hepatitis H and anti–liver–kidney microsomal antibodies for type 2. Although type 2 autoimmune hepatitis is seen in young children, it is extremely uncommon in infants.

This infant had received acetaminophen, reportedly in normal doses, and he had a low serum acetaminophen level, but an accidental overdose should always be considered. Hepatic injury from medications and toxins can be dose-dependent or idiosyncratic. Toxins that have been implicated in childhood cases of liver failure include *Amanita phalloides* (poisonous mushrooms) and organic solvents such as carbon tetrachloride and herbal medicines.[5] This patient had not been exposed to any of these toxins, and screening for toxins was negative.

We considered ischemic disease caused by occlusion of the hepatic veins (the Budd–Chiari syndrome), but this is generally associated with

dramatic hyperbilirubinemia, in addition to hepatomegaly and ascites. CT showed patent hepatic veins. Acute liver failure as a manifestation of hemophagocytic lymphohistiocytosis must also be considered in this age group; this patient had elevated ferritin and triglyceride levels and hypofibrinogenemia, but he did not have fever, splenomegaly, or cytopenias affecting more than one cell line, making this diagnosis unlikely.

The exclusion of these diagnoses leaves us with metabolic disorders. Metabolic disorders that manifest in early infancy are usually associated with cholestasis, which this infant did not have. In this older infant, fatty acid–oxidation defects, cholesteryl ester storage disease, glycogen storage diseases, and cystic fibrosis–related liver disease must be considered.[6] Wilson's disease, the most common metabolic disease that can present as acute liver failure in older children and adults, has not been reported in children younger than 3 years of age. This patient's age, the presence of fat detected on imaging of the liver, and the rapidly increasing size of the liver during the first few days of hospitalization led us to consider both fatty acid–oxidation defects and cholesteryl ester storage disorders. Despite his coagulopathy, we decided to pursue a liver biopsy to make a diagnosis.

PATHOLOGICAL DISCUSSION

Dr. Mikhail Lisovsky: A wedge biopsy of the liver was performed. The biopsy specimen showed diffuse severe steatosis (Fig. 2A, 2B, and 2C). A microvesicular pattern was seen predominantly in the centrilobular regions, and a macrovesicular pattern was present in the periportal areas. There was no evidence of hepatitis, hepatocellular necrosis, fibrosis, or ductular reaction, and no megamitochondria or polarizable material. A periodic acid–Schiff stain with diastase digestion showed no intracytoplasmic globules and no glycogen accumulation in hepatocytes. Stains for copper and iron and colloidal iron stain for mucopolysaccharides were negative. Electron microscopy confirmed the presence of abundant non–membrane-bound lipid vesicles in hepatocytes (Fig. 2D) and did not show abnormality of mitochondria, deposition of glycogen, or other storage products. A diagnosis of diffuse microvesicular and macrovesicular steatosis was made.

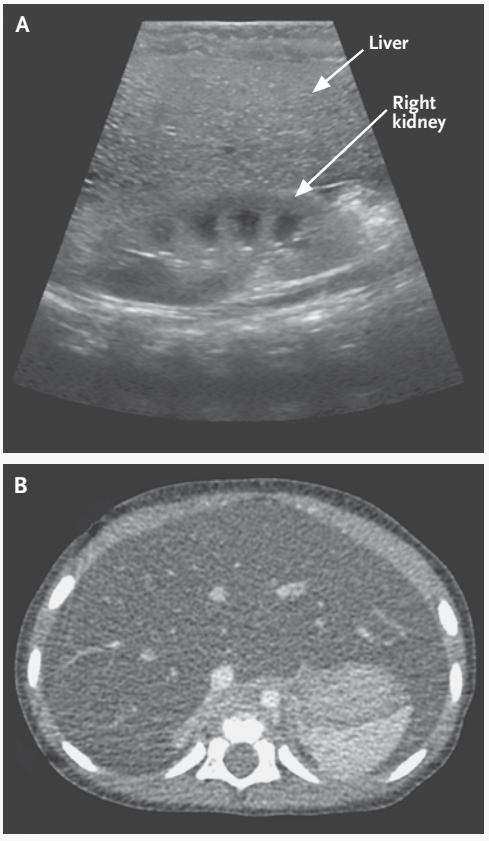

Figure 1. Abdominal Imaging Studies.
A sagittal sonographic view of the right hepatic lobe (Panel A) shows increased echogenicity of the liver parenchyma as compared with the adjacent kidney, which is compatible with fatty infiltration. An axial computed tomographic image of the abdomen (Panel B) shows a diffuse decrease in hepatic attenuation, which is also compatible with fatty infiltration.

Microvesicular steatosis is caused by impairment of mitochondrial function, in which decreased fatty acid beta-oxidation leads to accumulation of triacylglycerol and free fatty acids.[7] In this patient's age group, mitochondrial dysfunction is typically due to either an inherited metabolic error or an effect of a drug or toxin.[8] Inherited defects can involve mitochondrial systems of oxidative phosphorylation, fatty acid oxidation, or ureagenesis. Absence of periportal glycogenated nuclei, portal fibrosis, and aggregates of glycogenated hepatocytes argued against disorders of ureagenesis.[9] Ductular reaction and fibrosis, which are associated with abnormalities of mitochon-

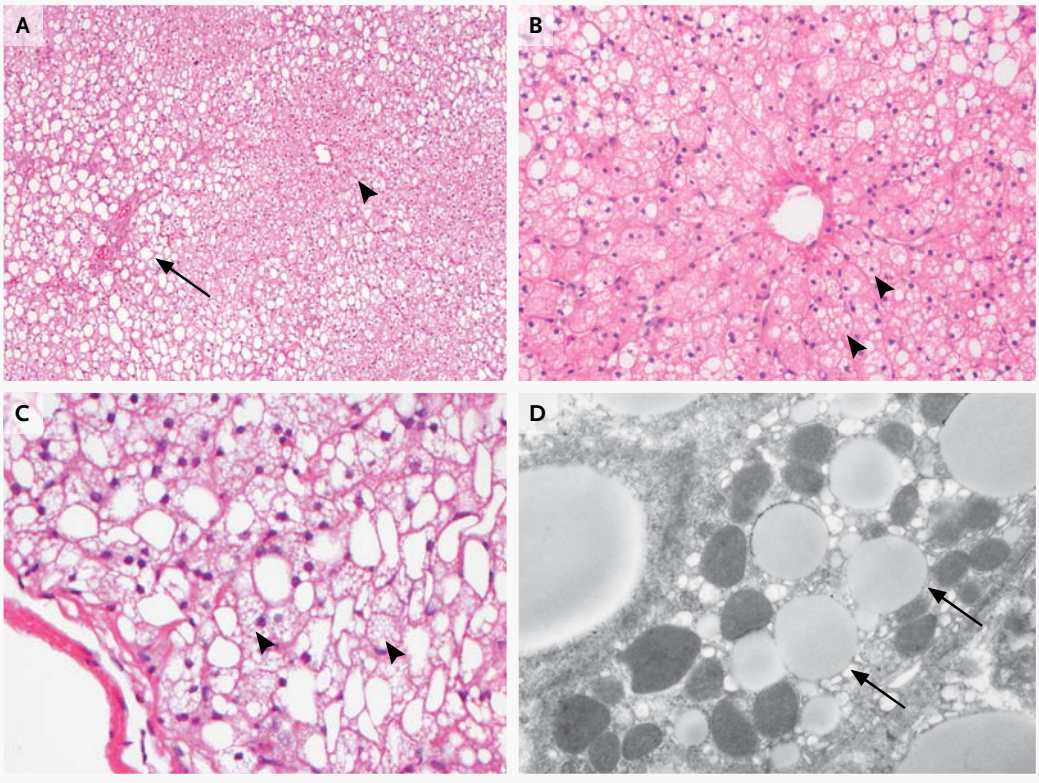

Figure 2. Liver-Biopsy Specimen.

At low magnification (Panel A), a microvesicular pattern of steatosis is present predominantly in the centrilobular region (arrowhead), and a macrovesicular pattern is present in the periportal areas (arrow). At higher magnification (Panel B), extensive microvesicular steatosis is present in the centrilobular area of the liver around the central venule (arrowheads). A subcapsular area (Panel C) shows extensive microvesicular steatosis (arrowheads). Ultrastructural examination (Panel D) shows a hepatocyte containing unremarkable mitochondria and non–membrane-bound lipid vesicles (arrows).

drial oxidative phosphorylation, were not noted.[10] Wolman's disease, caused by inactivity of lysosomal acid lipase, and cholesteryl ester storage disease, caused by reduced activity of lysosomal acid lipase, were considered, but the absence of foamy macrophages and Kupffer cells, polarizable cholesteryl ester crystals, fibrosis, and membrane-bound lipids and crystals on electron microscopy was not consistent with that diagnosis.[11]

Microvesicular steatosis could be caused by a drug or toxin, such as aspirin (Reye's syndrome), valproic acid, nucleoside analogues (such as didanosine and zidovudine), methylenedioxymethamphetamine, tetracycline, *Bacillus cereus* emetic toxin, acute iron overload, or poisoning. Reye's syndrome manifests as panacinar microvesicular steatosis in an older age group (4 to 15 years). Hepatocyte necrosis characteristic of *B. cereus* toxicity was not present.[12] Acute iron poisoning was ruled out by negative iron staining.[13] The remaining drug causes had been ruled out on clinical grounds.

Therefore, an inborn error of fatty acid beta-oxidation remained the primary consideration.

DIFFERENTIAL DIAGNOSIS

Dr. Fearing: The most likely inborn errors of metabolism that are suggested by this clinical presentation of a fatty liver in a 9-month-old infant are shown in Table 2.[14]

Fatty acid–oxidation defects and carnitine transport defects are generally suspected in a patient with hypoketotic hypoglycemia or in an infant, such as this one, with acute fatty liver. Fatty liver develops in infants with untreated fatty acid–oxida-

Table 2. Differential Diagnosis of the Inborn Errors of Metabolism Associated with Fatty Liver.*

Disease	Category	Gene and Locus	Enzyme Defect	Liver Findings	Other Findings
CPT2 deficiency	Carnitine cycle and fatty acid–oxidation defect	*CPT2* at 1p32	CPT2	Microvesicular steatosis	Progressive dilated cardiomyopathy
				Hepatomegaly	Hypoketotic hypoglycemia
Trifunctional protein deficiency	Fatty acid–oxidation defect	*HADHA* at 2p23 (trifunctional protein deficiency type 1, long-chain dehydrogenase deficiency)	Mitochondrial trifunctional protein with three components; long-chain dehydrogenase	Microvesicular steatosis	Hypoketotic hypoglycemia
		HADHB at 2p23 (trifunctional protein deficiency type 2)	Long-chain hydratase; long-chain thiolase	Hepatomegaly	
CACT deficiency	Carnitine cycle and fatty acid–oxidation defect	*SLC25A20* at 3p21.3	CACT	Hepatic failure	Hypoketotic hypoglycemia
				Microvesicular steatosis	Three forms: lethal neonatal, severe infantile hepatocardiomuscular, milder adult-onset (myopathy restricted)
Congenital disorder of glycosylation type Ib	Carbohydrate-deficient glycoprotein syndrome	*MPI* at 15q22-qter	Mannose-6-phosphate isomerase	Fibrosis; steatosis	Hyperinsulinemic hypoglycemia
				Hepatic failure	
Mitochondrial DNA depletion syndrome	Mitochondrial disorder	Mitochondrial deoxyguanosine kinase gene at 2p13	Mitochondrial deoxythymidine kinase (TK2)	Hepatomegaly	Hypotonia
				Abnormal liver-function tests	Lactic acidosis
				80 to 99% mitochondrial DNA depletion	Increased serum creatine kinase level
		Secondary association of *C10orf2* at 10q24		Micronodular cirrhosis	Multisystemic disease
				Cholestasis	Three forms: hepatocerebral, myopathic, benign later-onset myopathic or cardiomyopathic
				Steatosis	
				Jaundice	
				Hepatocellular necrosis	
				Pseudoacinar formation	
Wolman's disease and cholesteryl ester storage disease	Lipid-storage disease	*LIPA* at 10q24-q25	Lysosomal acid lipase	Hepatosplenomegaly	Onset in infancy (Wolman's disease)
				Hepatic fibrosis; foamy macrophages and Kupffer cells	Later onset (cholesteryl ester storage disease)

* CACT denotes carnitine acylcarnitine translocase, and CPT2 carnitine palmitoyltransferase II.

tion defects as well as in obligate carrier mothers, who are at increased risk for fatty liver of pregnancy.[15] Mitochondrial beta-oxidation is critical for generating energy from fats. Long-chain fats are escorted into the inner mitochondrial matrix by carnitine (β-hydroxy-γ-trimethylammonium butyrate).[16] Active transport across the outer mitochondrial membrane is mediated by carnitine palmitoyltransferase I (CPT1), traversing the outer to inner membranes by carnitine acylcarnitine translocase (CACT), and through the inner mitochondrial membrane by carnitine palmitoyltransferase II (CPT2). Within mitochondria, two carbons (acetyl coenzyme A [CoA]) are cleaved off the longer chain with each "turn" of the cycle until the long-chain fat is reduced to a final acetyl CoA. Acetyl CoA is used for ketogenesis, which is critical for energy during fasting, and the tricarboxylic acid cycle, which is used for energy at all times, especially by the heart and skeletal muscle. Defects in any of the enzymes involved in this pathway can result in accumulation of unoxidized fatty acids, resulting in intracellular accumulation of fat and a variety of organ dysfunctions.

This patient was well until 9 months of age, when acute liver failure suddenly developed in the context of a gastrointestinal illness. The fatty acid–oxidation defects that result in accumulation of long-chain fatty acids present with more severe clinical symptoms (hypoketotic hypoglycemia, liver disease, skeletal myopathy with or without cardiomyopathy, sudden death, and pregnancy complications) than the short-chain and medium-chain fatty acid–oxidation defects. The latter can have a more subtle onset, including decompensation with fasting, a more variable hypoketotic hypoglycemia, and skeletal myopathy. Nonetheless, even medium-chain deficiencies can be fatal in infancy.[17,18] Some patients are asymptomatic until an illness stresses the body's metabolic processing ability,[19] which may have been the case with our patient. In view of the severity of this patient's illness, I predicted a defect that would result in accumulation of very-long-chain fatty acids, such as CACT or CPT2 deficiency.

Elucidating the diagnosis in this suspected case of an inborn error of metabolism relies on "biochemical fingerprints" — an elevated level of a particular biomarker as a result of the enzyme deficiency. Testing in this case was done in parallel on both the archived original newborn screening panel obtained after parental consent and a fresh plasma sample.

DR. MARSHA KAY FEARING'S DIAGNOSIS

Fatty acid–oxidation defect (CACT vs. CPT2 deficiency).

PATHOLOGICAL DISCUSSION

Dr. Fearing: The analysis of the retrieved newborn screening panel showed elevated levels of acylcarnitine intermediates including C18:1/C18:1OH, C16/C16OH, C14, and a low free carnitine (C0). This pattern indicates CPT2 or CACT deficiency with a high probability. The plasma sample corroborated the newborn screening findings. These elevations included an increased C16 level of 2.6 nmol per milliliter (reference range, <0.5) and an increased C18 level of 0.59 nmol per milliliter (reference range, <0.12). The plasma total carnitine level was 18 μmol per liter (reference range, 38 to 68), and the free carnitine level was 2 μmol per liter (reference range, 27 to 49). Additional mitochondrial depletion studies showed a mean mitochondrial DNA content of 41% (within normal limits), making a nuclear-encoded mitochondrial deletion defect unlikely. The persistently abnormal carnitine levels strongly suggested a defect in the long-chain fatty acid–oxidation pathway and carnitine cycle.

Dr. Rapalino: A 3-tesla brain magnetic resonance imaging (MRI) study with magnetic resonance spectroscopy was performed on hospital day 5 because of the patient's altered mental status. The conventional T_2-weighted images show apparent "advanced" myelination of the white matter in the cerebral hemispheres as compared with an age-matched control infant (Fig. 3A and 3B), with no focal abnormalities. Single-voxel magnetic resonance spectroscopy obtained from the deep cerebral white matter shows prominent and well-defined abnormal lipid peaks at 1.4 and 0.9 ppm (Fig. 3C), as compared with the control (Fig. 3D), with relatively normal ratios of *N*-acetylaspartate to creatine and choline to creatine.

The radiologic differential diagnosis of these abnormal lipid peaks on magnetic resonance spectroscopy includes several disorders of lipid metabolism, including the Sjögren–Larsson syn-

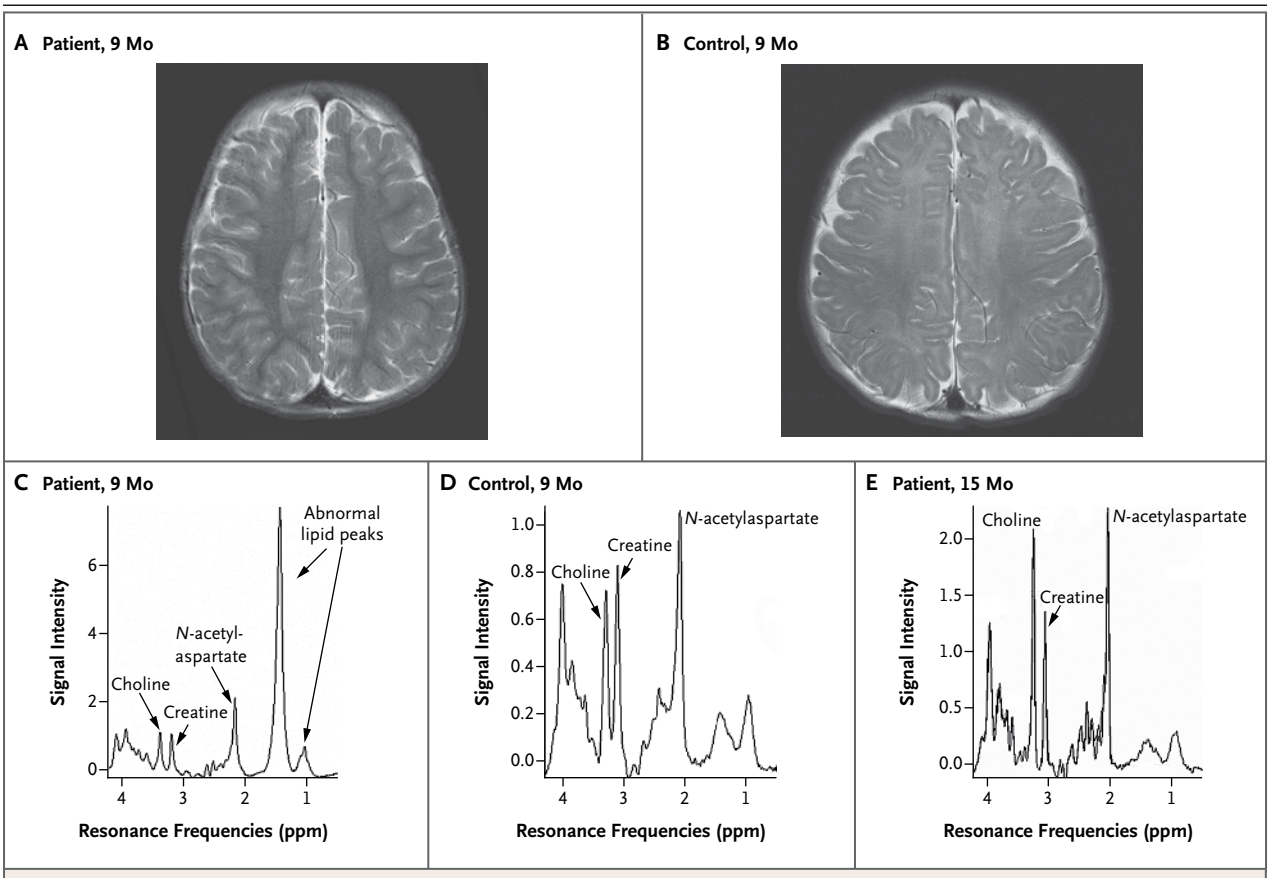

Figure 3. MRI and Magnetic Resonance Spectroscopy of the Brain.

T_2-weighted images show more extensive areas of decreased signal in the frontal and parietal white matter on MRI of the patient (Panel A) than on MRI of a healthy 9-month-old control subject (Panel B), suggesting advanced myelination in these regions. Magnetic resonance spectroscopy in the patient (Panel C) shows abnormal lipid peaks at approximately 1.4 and 0.9 ppm (arrows). These peaks are not seen on magnetic resonance spectroscopy in the healthy control subject (Panel D). The abnormal peaks are no longer seen on magnetic resonance spectroscopy performed when the patient was 15 months of age (Panel E).

drome (caused by deficiency of the microsomal fatty aldehyde dehydrogenase),[20-24] Zellweger's syndrome spectrum disorders (caused by mutations of *PEX* genes),[25-27] and CPT1 deficiency.[28]

This patient did not have signs of the Sjögren–Larsson syndrome (ichthyosis, mental impairment, and spasticity[23,29]) and did not have periventricular white-matter abnormalities or evidence of delayed myelination on conventional MRI.[23,21,22] The MRI findings also argue against Zellweger's syndrome spectrum disorders, which typically are associated with evidence of delayed myelination, abnormal cortical gyral patterns, and caudothalamic groove cysts on conventional MRI.[27,29-31] A case of CPT1 deficiency with a clinical presentation and magnetic resonance spectroscopic findings that were similar to those of this patient has been reported in the literature.[28]

Dr. Fearing: Additional testing was required to confirm the diagnosis. Options included functional enzyme assays performed in skin fibroblasts or muscle. However, these are very time-intensive studies and rely on adequate fibroblast growth, which can take up to 3 weeks from the skin-biopsy sample. Time for completion of the studies themselves can range from 3 to 8 weeks.[32]

Since the differential diagnosis was narrowed to CACT deficiency and CPT2 deficiency based on the biochemical analytes, we opted to sequence the genes for the two conditions in the laboratory of Dr. Lee-Jun C. Wong at the Medical Genetics Laboratories at Baylor College of Medicine. *CACT* (*SLC25A20*) gene-sequencing analysis revealed a F209X (*804delG*) mutation in exon 8, a previously reported pathogenic mutation[33]; a 160G→T (*G54W*) mutation in exon 2, which is predicted to be a

presumed pathogenic missense mutation by computer modeling; and a 163A→G (*T55A*) mutation in exon 2, presumed to be a benign variant by computer modeling. No mutations were detected in the *CPT2* gene.

This result established the diagnosis of CACT deficiency, an autosomal recessive disorder caused by mutations in both copies of the *SLC25A20* gene, as seen in this patient, resulting in insufficiency of the CACT enzyme. As a result, carnitine and acylcarnitine exchange across the mitochondrial membrane is disrupted. The clinical course in this age group is often severe, with neonatal seizures, cardiac arrhythmias, and apnea. There are fewer than 30 confirmed cases worldwide.[34,35]

Dr. Inderneel Sahai: This patient had a normal newborn screening panel, and yet when he was 9 months of age, an inborn error of metabolism was detected. Fatty acid–oxidation defects, including CACT and CPT2 deficiencies, can be identified in asymptomatic neonates by a characteristic pattern of elevated acylcarnitine levels, and thus they can be detected by newborn screening. However, the disorders included in the screening panel are determined according to the individual rules at play in the states where the child is born. They vary substantially (http://genes-r-us.uthscsa.edu) from state to state. To standardize screening nationwide, the American College of Medical Genetics recommends universal screening for 29 core conditions. An additional 25 secondary conditions are listed, for which it suggests that test results could be reported.[36] These secondary conditions are those that can easily be identified in the course of screening for core conditions but for which either the clinical significance or appropriate treatment is uncertain, and thus they are not ideal candidates for screening based on the Wilson–Jungner criteria, adopted by the World Health Organization (WHO).[37]

Although screening of newborns is mandated in the majority of U.S. states, most states allow parents to opt out of such screening.[38] Massachusetts mandates screening for conditions that meet the WHO criteria and offers optional screening (requiring parental consent) for other conditions, including acylcarnitine analysis.[39] This patient's mother had declined the optional expanded panel of tests.

This case underscores the importance of pursuing a clinical suspicion of metabolic disorders that are detectable by screening, despite normal results of newborn screening tests. A false negative screening result, although extremely rare, could occur because of an absence of analyte abnormalities due to temporal variations in its concentration, therapeutic interventions at the time when the specimen is collected, a specimen mix-up in the nursery, or a laboratory error. In this case, the normal result could have led us to consider Wolman's disease over a fatty acid–oxidation defect if the report had not been closely scrutinized to ascertain that the mother had declined the optional panel.

DISCUSSION OF MANAGEMENT

Dr. Fearing: Roughly 75% of carnitine is obtained from the diet from meat, dairy, and soybeans, and 25% is made through endogenous synthesis. This patient was treated by removing long-chain fats from the diet and supplementing his diet with oral carnitine. Ursodeoxycholic acid was also added by the gastroenterology service to reduce absorption of fats. Our long-term strategy will consist of a multidisciplinary team approach with a coordinated care clinic, a diet aimed at his enzymatic deficiencies, and oversight of biochemical genetics. The key will be avoidance of fasting, with frequent meals and a special diet with restriction of long-chain fatty acids.

Dr. Rapalino: At 15 months of age, repeated magnetic resonance spectroscopy showed resolution of the abnormal lipid peaks seen at the time of the diagnosis (Fig. 3E).

Dr. Fearing: The patient is now almost 3 years of age and is growing and thriving. He has done well on the dietary restriction of long-chain fatty acids, starting with an elemental formula as an infant, and progression to foods with 10% essential fatty acids, supplemental carnitine, and ursodeoxycholic acid. He is in the 50th percentile for height and weight and the 35th percentile for head circumference. He has met all developmental milestones.

Dr. Nancy Lee Harris (Pathology): Are there any questions?

Dr. Ronald E. Kleinman (Pediatrics): One of the many extraordinary findings in this case was the apparently enhanced myelination on MRI. What caused that?

Dr. Rapalino: The cause of this finding is not

clear. It is possible that the presence of abnormal lipid metabolites could be responsible for the apparent extensive bilateral "advanced" myelination of the deep and subcortical white matter in this patient. Unilateral areas of advanced myelination have been reported in patients with the Sturge–Weber syndrome[5,40] and hemimegalencephaly[41] or more extensively in cases of the sudden infant death syndrome.[42] However, data on apparent advanced myelination bilaterally in the deep and subcortical white matter in patients with disorders of lipid metabolism are lacking.

ANATOMICAL DIAGNOSIS

Microvesicular hepatic steatosis due to CACT deficiency.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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