Brief Report

A Defect in the Transport of Long-Chain Fatty Acids Associated with Acute Liver Failure

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FATTY-ACID oxidation has a major role in energy production during periods of fasting. When body glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver, and converted to ketone bodies, a major alternative source of energy for peripheral tissues.[1] At the cellular level, after being transported through the cell membrane and then into the mitochondria by means of a carnitine-dependent system, long-chain fatty acids are predominantly oxidized in mitochondria.[2,3]

Common clinical features of disorders of fatty-acid oxidation are metabolic decompensation during fasting, hypoketotic hypoglycemia, and acute dysfunction of fatty-acid–dependent tissues (skeletal muscle, heart, and liver), often leading to sudden death in early life.[4-6] Although understanding of the biochemical and molecular bases of these disorders has improved dramatically in recent years, affected patients are often given a diagnosis of an unspecified disorder of fatty-acid oxidation.[7] The study of such patients has provided valuable insights into the oxidative process.[8-10] We describe two young boys who presented with acute liver failure and were found to have a defect in the transport of long-chain fatty acids.

CASE REPORTS

Patient 1

Patient 1 was a one-year-old white boy born at term to unrelated parents. He presented with symptoms of a viral illness, nonketotic hypoglycemia (blood glucose, 7 mg per deciliter [0.39 mmol per liter]), hyperammonemia (plasma ammonia, 122 μg per deciliter [87 μmol per liter]), and acute hepatic failure. Intravenous glucose and supportive therapy were given, and he gradually recovered. The results of standard evaluations for hepatic failure, including viral studies and toxicologic screening, were negative.[11]

During the next four years, the child had seven additional episodes of acute liver failure characterized by elevated serum aminotransferase levels (range of peak alanine aminotransferase, 3690 to 9900 U per liter), coagulopathy (range of prothrombin time, 15 to 86 seconds), and hyperbilirubinemia (range of serum total bilirubin, 2.1 to 8.1 mg per deciliter [36 to 139 μmol per liter]). Some of the episodes were associated with hyperammonemia (range of plasma ammonia, 42 to 165 μg per deciliter [30 to 118 μmol per liter]) and mild encephalopathy; no clinical or laboratory evidence of cardiac or skeletal myopathy was found. Between episodes the child was well, and his growth and development were normal. He was treated empirically with frequent feedings of a low-fat (fat, <20 percent of total calories) diet supplemented with 1.75 g of medium-chain triglyceride oil per kilogram of body weight per day. From three to five years of age, he also received carnitine supplements (100 mg per kilogram per day) intermittently.

At five years of age, he had his most severe episode, with the development of hepatic encephalopathy and, over a period of 24 days, steady increases in serum total bilirubin (up to 25 mg per deciliter [428 μmol per liter]) and persistent coagulopathy. He underwent orthotopic liver transplantation. His postoperative course was complicated by a bile-duct stricture, placement and multiple replacements of a drainage stent tube, and finally, surgical reconstruction of the bile duct. At the most recent follow-up visit two years after transplantation, the patient was 7½ years old and in good health. The serum total bilirubin level was 0.4 mg per deciliter (8 μmol per liter), and the serum alanine aminotransferase level was 47 U per liter.

Patient 2

Patient 2 was a four-year-old white boy who had been in good health and who presented with otitis media, which was treated with amoxicillin, and several episodes of vomiting. Physical examination revealed scleral icterus, jaundice, and hepatomegaly, with a soft liver palpable 4 to 5 cm below the right costal margin. The results of a neurologic examination were normal. The serum total bilirubin level was 5.7 mg per deciliter (97 μmol per liter), with a serum conjugated bilirubin level of 3.9 mg per deciliter (67 μmol per liter), a serum alanine aminotransferase level of 3179 U per liter, a prothrombin time of 14.6 seconds, and a plasma ammonia level of 23 μg per deciliter (33 μmol per liter). The results of viral studies and toxicologic tests were negative.

Liver failure and mild encephalopathy developed that were characterized by hyperammonemia (plasma ammonia, 168 μg per deciliter [120 μmol per liter]) and hyperbilirubinemia (serum total bilirubin, 26 mg per deciliter [445 μmol per liter]). The serum alanine aminotransferase level decreased to 429 U per liter, whereas the prothrombin time increased (to 35 seconds). The patient underwent successful orthotopic liver transplantation. At the most recent follow-up visit one year after transplantation, the child was in good health, with a serum total bilirubin level of 0.4 mg per deciliter (7 μmol per liter) and a serum alanine aminotransferase level of 13 U per liter.

METHODS

Biochemical and Histologic Studies

Quantitative analyses of metabolites in liver tissue from Patient 1 and control liver tissue were performed according to established methods.[6,12] The liver findings in the patient were compared with those obtained from 5 unused segments of reduced-size liver transplants (provided by Dr. Peter F. Whitington, University of Chicago, Chicago) and 10 samples obtained post mortem from patients with disorders of fatty-acid oxidation.[6] Liver-tissue slides

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were examined with use of the following stains: hematoxylin and eosin, trichrome, periodic acid–Schiff, iron, and oil red O.

Cell Lines and Enzyme Assays

The study was approved by the Yale human investigation committee. Skin-biopsy specimens were obtained from both patients after written parental consent. We also obtained as controls cultured skin fibroblasts from three normal cell lines (Coriell Cell Repositories, Camden, N.J.), a patient with a carnitine-uptake defect, a patient with carnitine palmitoyltransferase I deficiency, a patient with carnitine palmitoyltransferase II deficiency, and a patient with long-chain 3-hydroxyacyl–CoA dehydrogenase deficiency. Fibroblasts were maintained in minimal essential medium supplemented with 10 percent fetal-calf serum, 2 mM glutamine, and antibiotics. Oxidation rates of [^{3}H]myristate, [^{3}H]palmitate, and [^{14}C]oleate were measured as previously described.[13,14] Cell membranes were made permeable by the addition of 0.01 percent digitonin to the incubation medium.

For uptake studies, tritiated ([9,10-^{3}H(N)]) C_{14} to C_{20} fatty acids, [^{14}C]2-deoxy-D-glucose, [^{14}C]carnitine, and [^{14}C]palmitoyl–carnitine were obtained from Dupont–New England Nuclear (Wilmington, Del.). The uptake of tritiated fatty acids was measured according to the method of Schaffer and Lodish.[15] To each well of a multi-well incubation plate, 1 μCi of arachidonic acid, 5 μCi of oleic acid, 5 μCi of palmitic acid, or 10 μCi of myristic acid was added. Two sets of plates were analyzed in each experiment; one was assayed at 37°C, and the second set was incubated at 0°C for the purpose of determining nonspecific membrane binding. The uptake of [^{14}C]2-deoxy-D-glucose, [^{14}C]carnitine, and [^{14}C]palmitoyl–carnitine (2.5 μCi of each) was studied according to previously described methods.[16,17]

RESULTS

The initial findings for Patient 1 suggested an underlying disorder of fatty-acid oxidation. However, biochemical analysis of urine and plasma specimens collected during acute illnesses showed minimal accumulation of dicarboxylic acids, acylglycines, or acylcarnitines; plasma levels of total and free carnitine were occasionally reduced, with no elevation of the esterified fraction. When plasma free fatty acids were measured during the final episode in Patient 1 and the only episode in Patient 2, the values were elevated (1.8 and 1.6 mmol per liter, respectively; normal range, 0.5 to 1.5). When Patient 1 was evaluated between episodes, values of 0.16 and 0.45 mmol per liter were recorded. In the case of Patient 2, his only other detectable biochemical abnormality at presentation was a low plasma level of free carnitine (9 μmol per liter; normal range, 24 to 63), with an esterified fraction of 2 μmol per liter.

Although these results ruled out the majority of known disorders of mitochondrial fatty-acid oxidation, the rates of oxidation of myristic acid, palmitic acid, and oleic acid in cultured skin fibroblasts were abnormal, particularly in Patient 1 (Table 1). The severity of the compromise of the oxidative flux was apparently correlated with the length of the substrate. Specific assays for many mitochondrial enzymes, from carnitine palmitoyltransferase I to long-chain 3-keto-acyl–CoA thiolase (the β-subunit of the trifunctional protein), revealed normal activity in cultured skin fibroblasts from both patients (data not shown).

TABLE 1. RATES OF FATTY-ACID OXIDATION IN CULTURED SKIN FIBROBLASTS.*

SUBSTRATE (CHAIN LENGTH)	INTACT FIBROBLASTS		PERMEABILIZED FIBROBLASTS		
	PATIENT 1	PATIENT 2	PATIENT 1	PATIENT 2	NORMAL SUBJECTS†
	percent of normal‡		pmol/min/mg of protein		
Myristic acid ($C_{14:0}$)	68	77	2.9	1.4	0.42, 1.20
Palmitic acid ($C_{16:0}$)	32	67	10.9	5.6	6.28, 6.60
Oleic acid ($C_{18:1}$)	20	ND	ND	ND	ND

*ND denotes not determined.

†Values are the medians for three normal subjects in two separate experiments.

‡Values indicate the percentages of the median values for three normal subjects.

One month after the initial episode in Patient 1, a needle biopsy of the liver showed patchy necrosis of hepatocytes. The residual hepatocytes were markedly swollen and vacuolated in the presence of mild, chronic portal inflammation (Fig. 1A). Electron microscopy revealed moderate steatosis with increased levels of glycogen and ultrastructural features suggestive of nonspecific hepatocellular injury, such as dilatation of the smooth endoplasmic reticulum, normally shaped mitochondria with unremarkable cristae, and dense granules in the matrix. These findings were inconsistent with a diagnosis of Reye's syndrome or viral hepatitis but did not rule out an underlying metabolic disorder or toxin-induced liver injury.[11]

An open liver biopsy was performed when Patient 1 was four years old and asymptomatic (serum alanine aminotransferase, 55 U per liter; serum total bilirubin, 0.7 mg per deciliter [12 μmol per liter]; prothrombin time, 12.5 seconds; plasma ammonia, 54 μg per deciliter [39 μmol per liter]; and plasma free fatty acids, 0.09 mmol per liter). Morphologic evaluation showed only mild fibrosis around the portal tracts and focal vacuolization of hepatocytes in otherwise normal tissue (Fig. 1B). Analysis of the explanted liver (Fig. 1C and 1D), which was removed when the patient was five years old, revealed markedly abnormal hepatic parenchyma, with irregular sinusoidal fibrosis (confirmed by trichrome and reticulin stains), regenerative changes, and vacuolar degeneration. Staining with oil red O showed nonspecific extracellular staining of fat droplets, with only occasional cells containing microvesicular fat droplets. In Patient 2, the explanted liver showed massive hepatocellular necrosis, bile-duct proliferation, and collapsed fibrosis. Staining with oil red O revealed mild deposition of fat globules in the cytoplasm of a few hepatocytes and in the interstitium.

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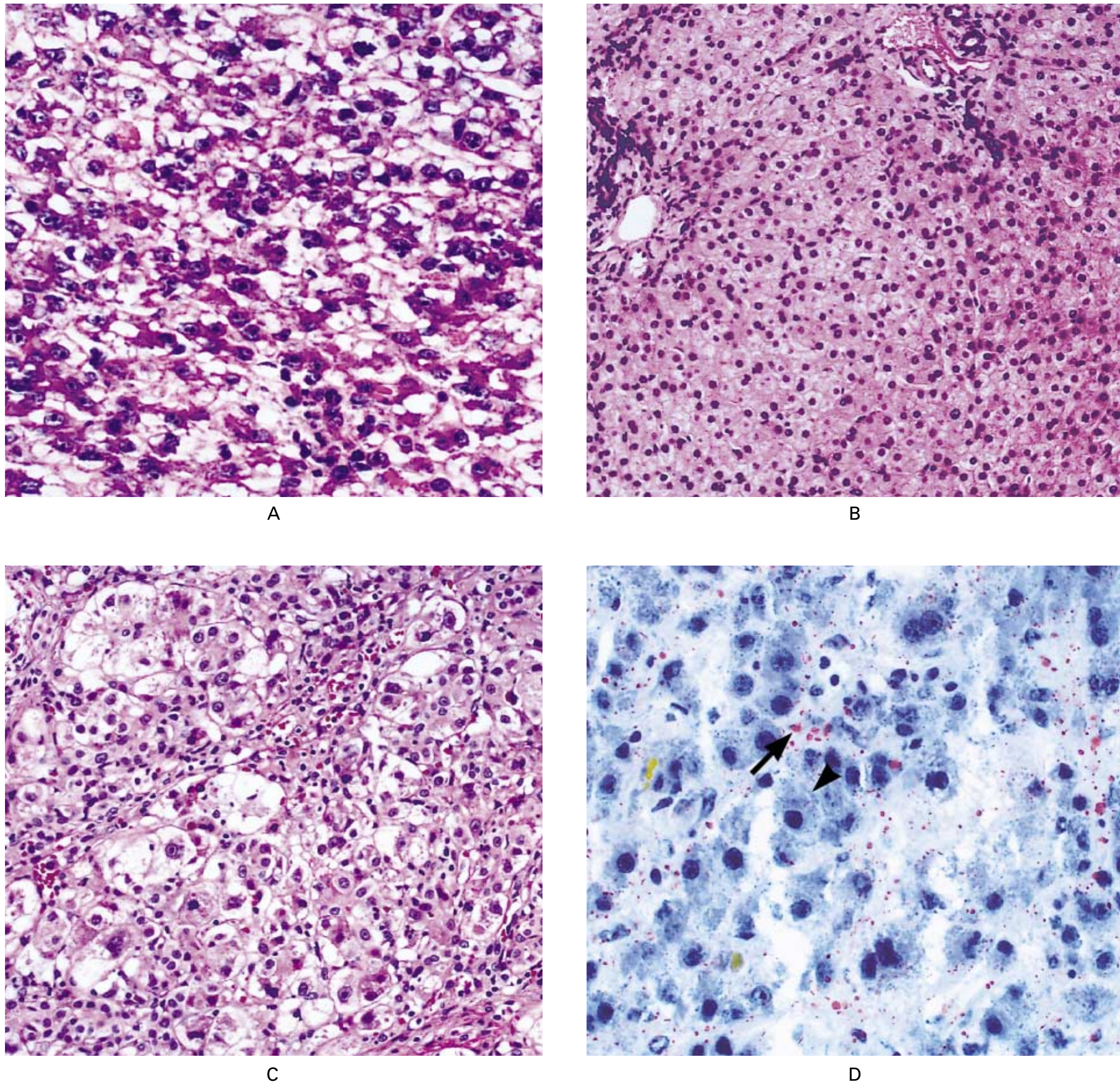

Figure 1. Morphologic Appearance of Liver Tissue from Patient 1.

In Panel A, the initial liver-biopsy specimen shows diffuse hepatocellular damage with degeneration due to edema, multivesicular cytoplasmic vacuolization without nuclear displacement, a pseudoacinar arrangement, and focal necrosis (hematoxylin and eosin, ×400). Panel B shows a biopsy specimen obtained during a clinically quiescent period when the patient was four years old, one month after an episode of liver failure. The morphologic findings are essentially unremarkable, with only minimal portal fibrosis and hepatocellular vacuolization (hematoxylin and eosin, ×200). In Panel C, a section of explanted liver shows loss of architecture, hepatocellular damage with cytoplasmic vacuolization, a pseudoacinar arrangement, cholestasis, and diffuse interstitial fibrosis (hematoxylin and eosin, ×200). In Panel D, a section of explanted liver stained with oil red O shows scattered fat droplets (red dots) that are present mainly extracellularly (arrow); the arrowhead points to the cytoplasm of a representative hepatocyte without detectable accumulation of fat (×400).

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Levels of free fatty acids and carnitine were measured in tissue from the open liver biopsy in Patient 1. The tissue homogenate revealed a distinctive profile, characterized by low levels of myristic acid, palmitic acid, stearic acid, oleic acid, and linoleic acid and elevated levels of carnitine (Table 2). This pattern was essentially the opposite of those typically found in patients with other disorders of fatty-acid oxidation (Table 2).[6]

In the light of these results, a defect in the transport of long-chain fatty acids at the plasma-membrane level appeared likely, and oxidation experiments were repeated after permeabilization of fibroblast membranes with digitonin. In cells from both patients, the oxidation rate was similar to or higher than that of normal subjects (Table 1). For comparison, a cell line from a patient with a deficiency of mitochondrial long-chain 3-hydroxyacyl–CoA dehydrogenase showed similar rates of palmitate oxidation before and after membrane permeabilization (20 percent and 22 percent, respectively, of the mean value of controls tested simultaneously).

The uptake of oleic acid ($C_{18:1}$) in skin fibroblasts from the patients was lower than that in control cells (Table 3). As was true for the oxidation results, the severity of the defect was correlated with the length of the fatty acid tested (Table 3). To ascertain that the observed deficit was not caused by a generalized impairment of transport at the plasma-membrane level, the uptake of carnitine and 2-deoxy-D-glucose was measured in both patients and was normal (Table 3).

Longo et al. have recently shown that palmitoyl–carnitine is also a substrate for the plasma carnitine transporter and that the affinity for this substrate is higher than that for the physiologic substrate.[18] Unlike the uptake of palmitic acid by fibroblasts from the patients, the uptake of palmitoyl–carnitine was normal (Table 3), providing further evidence of a defect in the transport of long-chain free fatty acids. The uptake of oleic acid was normal or nearly normal in skin fibroblasts from all three patients with other disorders of fatty-acid oxidation, whereas the uptake of both carnitine and palmitoyl–carnitine was reduced, as expected, in the patient with carnitine-uptake defect.

Table 2. Levels of Free Fatty Acids and Carnitine in Liver Homogenate.

Metabolite	Patient 1		Patients with Other Disorders of Fatty-Acid Oxidation*		Normal Subjects†	
	value	percent of normal	range	median	range	median
	μmol/100 mg of protein		μmol/100 mg of protein			
Myristic acid	0.01	20	0.2–9.5	0.9	0.02–0.11	0.05
Palmitic acid	1.3	27	5.7–35.5	13.8	3.1–5.9	4.8
Stearic acid	0.6	50	2.4–8.3	3.4	1.0–1.3	1.2
Oleic acid	0.7	14	4.2–30.0	9.0	3.6–6.6	5.1
Linoleic acid	0.5	24	2.2–74.0	7.7	1.9–2.7	2.1
Carnitine‡	1.7	212	0.3–1.2	0.5	0.6–1.1	0.8

*Liver specimens were obtained post mortem from five patients with very-long-chain acyl–CoA dehydrogenase deficiency and five patients with long-chain 3-hydroxyacyl–CoA dehydrogenase deficiency, and all values were confirmed by enzymatic or molecular analyses (or both).[6]

†Values were obtained in five unused segments of reduced-size liver transplants.

‡Results are expressed as micromoles per gram of wet weight.

DISCUSSION

Fatty-acid oxidation is a complex process that begins with the transport of fatty acids through the plasma membrane. Although there is a general consensus that short-chain and medium-chain fatty acids (C_4 to C_{12}) diffuse freely across plasma and mitochondrial membranes, the mechanism of transport of longer-chain species (C_{14} to C_{20}) has been the object of intense debate. At least five different transporters of long-chain fatty acids have been characterized in different species at the protein or gene level,[15,19-22] but whether active transport actually occurs is controversial. There are conflicting theories of the way in which long-chain fatty acids penetrate the cell membrane.[2,23-25] The degree of biochemical and molecular characterization of putative fatty-acid transporters varies considerably, and our understanding of their similarities across species, expression in tissues, substrate specificity, and regulation is limited. To our knowledge, none of the transporters described thus far have been linked directly or indirectly to disease in humans.

Disorders of the oxidation of long-chain fatty acids are characterized by fasting-induced hypoketotic hypoglycemia, fatty infiltration of parenchymal organs, and either acute liver dysfunction or myopathy, with potentially severe cardiac involvement.[4-6,12] The clinical course of Patient 1 was characterized by several episodes of acute hepatic failure followed by a life-threatening event that required orthotopic liver transplantation. Patient 2 had a single but extremely severe episode of acute hepatic failure, which also required liver transplantation. The precise mechanism of the liver injury remains to be determined.

As underscored by recent reports,[8-10] some disorders of fatty-acid metabolism represent a major diagnostic challenge, because of tissue-specific expression of the defective enzyme, unexpected biochemical phenotypes, or the absence of detectable biochemical markers in blood and urine even at the time of acute illness. In our patients, the failure of extensive biochemical investigations to reveal abnormal levels of metabolites in plasma and urine, together with

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TABLE 3. UPTAKE OF VARIOUS SUBSTRATES IN CULTURED SKIN FIBROBLASTS.*

SUBSTRATE (CHAIN LENGTH)	PATIENT 1	PATIENT 2	PATIENTS WITH OTHER DISORDERS OF FATTY-ACID METABOLISM			NORMAL SUBJECTS†	
			CUD	CPT I	CPT II	MEAN ±2 SD	RANGE
	pmol/min/mg of protein (% of normal)					pmol/min/mg of protein	
Myristic acid ($C_{14:0}$)	3.3 (92)	3.4 (94)	3.5 (97)	ND	ND	3.6±0.7	3.3–4.1
Palmitic acid ($C_{16:0}$)	1.8 (50)	2.6 (72)	3.2 (89)	ND	ND	3.6±0.5	3.3–3.9
Oleic acid ($C_{18:1}$)	1.0 (34)	1.8 (62)	2.4 (83)	2.6 (90)	2.4 (83)	2.9±0.4	2.7–3.0
Arachidonic acid ($C_{20:4}$)	2.4 (45)	3.7 (70)	ND	ND	ND	5.3±0.5	5.1–5.7
Carnitine	0.91 (102)	0.84 (94)	0.02 (2)	0.86 (97)	0.91 (102)	0.89±0.12	0.80–0.96
Palmitoyl–carnitine	39.8 (105)	38.3 (101)	11.8 (31)	ND	ND	37.9±2.6	36.2–39.5
2-Deoxy-D-glucose	180 (100)	163 (91)	169 (94)	166 (92)	170 (94)	180±40	160–200

*For all patients, the mean value of three separate experiments performed in triplicate is shown. CUD denotes carnitine-uptake defect, CPT I carnitine palmitoyltransferase I deficiency, CPT II carnitine palmitoyltransferase II deficiency, and ND not determined.

†Values were obtained in three separate experiments performed in triplicate for each of three cell lines.

the finding of abnormal fatty-acid oxidation in vitro, raised the suspicion of a defect located upstream of the transport of long-chain fatty acids through the mitochondrial membranes.[3] This hypothesis was confirmed by the finding that the oxidation of myristic acid and palmitic acid increased after plasma-membrane permeabilization, by the correlation between the severity of the defect and the length of the substrate tested, and by the presence of normal uptake of other substrates. Previously, a disorder involving a defective plasma-membrane carnitine transporter, which impairs the uptake of carnitine in the kidney, muscle, and skin fibroblasts, but not in liver, has been reported.[17]

Of particular interest was the absence of fatty infiltration of the liver in our patients, a finding that was initially interpreted as incompatible with an underlying disorder of fatty-acid oxidation. A number of children with acute or fulminant liver failure and atypical liver histologic findings have been described.[26-29] In one study,[29] seven patients had clinical and morphologic features similar to those of our patients and four also had unspecified patterns of dicarboxylic aciduria, but an underlying disorder of fatty-acid oxidation was considered unlikely because of the absence of abnormal biochemical findings after the patients recovered.

Our report should lead to both retrospective and prospective identification of additional patients with the same disorder and eventually to a better understanding of the underlying mechanisms of this disease. Although extensive studies will be needed to pinpoint the molecular basis of this disorder, the finding of a defect in fatty-acid uptake with severe clinical manifestations supports the view that active transport of long-chain fatty acids is required in infants and young children to maintain hepatic ketogenesis and energy supply during fasting.

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