Article abstract

An 11-year-old boy had had recurrent episodes of hepatic and cerebral dysfunction and underdeveloped musculature. Overt weakness developed at age 10. Lipid excess, especially in type I fibers, was found in muscle. Hypertrophied smooth endoplasmic reticulum and excessive microbodies were present in liver. Marked carnitine deficiency was shown in skeletal muscle, plasma, and liver. Ketogenesis was impaired on a high fat diet, but omega oxidation of fatty acids was enhanced. There was excessive glucose uptake and essentially no oxidation of labeled long-chain fatty acids by perfused forearm muscles *in vivo*. Oral replacement therapy restored plasma carnitine levels to normal, but not liver or muscle carnitine levels, and was accompanied by clinical improvement.

The syndrome of systemic carnitine deficiency

Clinical, morphologic, biochemical, and pathophysiologic features

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In 1972 Engel and Siekert described an unusual variety of lipid storage myopathy in a 24-year-old woman.¹ The unusual features included a striking beneficial response to corticosteroid therapy and the coexistence of abnormal liver function tests. Subsequently, Engel and Angelini found that the skeletal muscle of this patient had a very low level of carnitine, and *in vitro* oxidation of fatty acids by her muscle was considerably reduced.^{2,3} This patient was the first recognized human example of carnitine deficiency. Since that report, at least four other patients have been identified.⁴⁻⁷

This paper is a detailed report of a patient with systemic carnitine deficiency,⁴ with special attention to the varied clinical, morphologic, biochemical, and metabolic features of this disorder.

Case report. This 11-year-old boy was born after a full term uneventful pregnancy and delivery. Birth weight was 7 lb. Milestones of his psychomotor development were normal, but according to his mother, he was always a "weak and clumsy child" and his neck and head were always "floppy."

At age three and one-half years, the patient was hospitalized with acutely developing vomiting and a major convulsive seizure. Cerebrospinal fluid was normal, as was serum calcium. His blood sugar was reduced initially to 27 mg percent but subsequently was found to be normal on several occasions. He had some abnormal liver function tests; serum glutamic oxaloacetic transaminase (SGOT) 103 units (normal, less than 30) and serum glutamic pyruvic transaminase (SGPT) 125 units (normal, less than 25 units), but serum bilirubin was normal. An electroencephalogram (EEG) showed a diffuse, high amplitude dysrhythmia. The cause of the acute encephalopathy and the abnormal liver function tests was not established and the child's clinical status, EEG, and liver function tests returned to normal.

The patient started school at age six, but after completing grades 1 and 2 he had difficulties with writing and spelling. Psychometric evaluation revealed an intelligence quotient of 99, with impairment in perceptual motor integration and form discrimination and an immature body image and laterality. He was enrolled in a remedial teaching program and has made good progress.

At nine years of age he developed acute confusion and stupor and was found to have moderate hepatic enlargement. Blood sugar now was normal but liver function tests again were impaired: SGOT 205 units, SGPT 175 units, lactic

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dehydrogenase 1,800 units (normal, less than 240 units). Search for Australia antigen was negative. The patient was considered to have had acute hepatic encephalopathy due to Reye's syndrome. In two months his clinical status, liver size, and liver function tests returned to normal. His general level of neuromuscular functioning was adequate. He could walk a mile and played baseball and hockey, albeit somewhat clumsily.

In the spring of 1973, at age 11 years, a gradual development of muscle weakness was noted. He walked slowly and often stumbled and he no longer could run. Within months he could not walk to school a few blocks away, nor could he play outdoors. He became short of breath after walking half a block. He was always fatigued and his appetite declined.

Family history shows no consanguinity between his parents, who show no signs of disease. His 16-year-old brother is normal. A sibling died when 15 months old as a consequence of pathologically proved congenital biliary atresia.

In the summer of 1973 the patient (age 11 years) was a thin, frail child with stunted growth (figure 1). His weight was 20 kg (less than the third percentile), his height 130 cm (less than the third percentile). He had a high arched palate and small fifth fingers. The liver edge was palpable 3 cm below the right costal margin. His spleen was not enlarged. He had an elongated face with hypotonic and weak musculature and mild bilateral ptosis. Extraocular movements were intact. The temporalis muscle showed atrophy and weakness. The neck muscles were thin and weak, and he could hardly hold his head up when standing. His head moved in a "rag doll" manner when walking. The limb muscles showed considerable atrophy and moderate weakness, more proximally than distally. Marked winging of the scapulae was noted. There was considerable lumbar lordosis and a waddling gait, and Gower's sign was positive. He could not walk stairs without holding onto railings, nor run, stand on one leg, or hop. The tendon reflexes were present but subdued throughout. No muscle tenderness, fasciculation, percussion myotonia, or cramps were observed, and there were no sensory deficits.

Laboratory findings were normal on the following tests: Routine hemogram: erythrocyte sedimentation rate, urinalysis, urinary amino acid profile by paper chromatography, blood electrolytes, serum protein electrophoresis and immunoelectrophoresis, serum bilirubin, cholesterol and triglycerides, creatine phosphokinase, chest radiography, electrocardiogram, and electroencephalogram.

The following laboratory results were abnormal: SGOT was 376 units. Electromyography showed short duration and small amplitude and polyphasic motor units in some areas of proximal muscles of the limbs. There was no spontaneous activity. Nerve conductions were normal.

Materials and methods. Biopsies of the left vastus lateralis and rectus abdominis muscles of the patient were taken under general anesthesia before carnitine administration and a biopsy of the left biceps was obtained under local anesthesia 5 months after carnitine supplement. Biopsies of the left biceps muscle also were obtained under local anesthesia from each parent; all muscle biopsies were studied with histochemistry and electron microscopy. Two liver biopsies were obtained from the patient, the first by a small incision laparotomy before carnitine administration and the second by a percutaneous needle puncture after 5 months of carnitine replacement therapy. Aliquots of tissue specimens and heparinized plasma samples from the patient and his parents were frozen and kept for a few days at -30°C

Figure 1. Patient at age 11 years, before carnitine replacement.

until carnitine levels were determined by the method of Fritz and Marquis⁸ (muscle) and of Cederblad and Lindstedt⁹ (plasma and liver). Noncollagenous protein in muscle and liver was measured by the Lowry¹⁰ method after digestion of the tissue by the procedure of Lilienthal and co-workers.¹¹ Plasma carnitine level also was determined in the patient, $\frac{1}{2}$, 1, 2, 3, and 8 hours after a single oral dose of 500 mg DL carnitine (Sigma®). (Lack of carnitine toxicity was established by feeding 300 gm Sprague-Dawley rats 1 gm of the same lot of DL carnitine daily for 5 days. There were no noticeable clinical or pathologic effects on the vital organs of the animals.)

Urinary dicarboxylic acids, lactic acid, beta hydroxybutyric acid, and parahydroxyphenylacetic acid were determined with a coupled gas chromatograph and mass spectrometer by the method of Mamer, Crawhall, and Tjoa¹² in various urine samples of the patient. Samples included a random urine sample on regular diet, 2 hours after a high carbohydrate diet, and after a 72-hour administration of an isocaloric ketogenic diet. Random urine samples from the parents were similarly studied.

In vivo forearm metabolic studies to measure blood flow, oxygen consumption, glucose and long-chain fatty acid utilization were performed on the patient by the technique of Klassen, Andrews, and Becklake¹³ in the fasting state. Because of the small size of the forearm, a No. 21 Riley arterial needle was used to cannulate the left brachial artery for infusion of indicators, and the right brachial artery to sample arterial blood. Venous blood

was obtained from a soft plastic catheter inserted retrograde to flow into the left antecubital vein. During sampling and infusions of labels, the hand was excluded from the circulation by a cuff maintained at a pressure greater than arterial pressure. After the needles were inserted under local anesthesia, constant infusion of Evans blue dye was started to measure blood flow. Sample sets were obtained during a control period, during forearm exercise consisting of flexion of the hand at the wrist, and on three occasions during an infusion of C^{14} -oleic acid ($0.01 \mu\text{Ci}$) and C^{14} -linoleic acid ($0.01 \mu\text{Ci}$). Each infusion lasted approximately 20 minutes, with a 10-minute rest period between them. The techniques of handling samples, processing the blood, and analytical procedures were previously described.¹³ Oxygen content was measured by the method of Sabatier,

Skinner, and Balcavage¹⁴ and $C^{14}\text{O}_2$ was measured by the technique of Stuart and Williams.¹⁵

The conversion of gamma butyrobetaine to carnitine was determined in vitro by the method of Lindstedt and Lindstedt¹⁶ in 70,000 g supernatant fractions of homogenates of the patient's first liver biopsy.

Results. *Histology and histochemistry.* Muscle. The quadriceps and the rectus abdominis muscles of the patient showed similar findings. Almost all histochemical type I fibers contained numerous 1 to 4μ large round or 15 by 2μ slitlike spaces filled with neutral fat (figure 2). About one-third of these fibers were significantly atrophic and somewhat angular. The spaces containing the neutral fat appeared optically empty if a lipid solvent was used in the staining technique (figures 3 and 4).

Figure 2. Sudan black B, $\times 350$. (A) Quadriceps; considerable accumulation of lipid is present in many type I muscle fibers. (B) Biceps; lipid excess and atrophy is less prominent than in quadriceps.

Figure 3. All cryostat sections, modified trichrome, $\times 350$. (A) Quadriceps; many, mostly atrophic, fibers harbor vacuoles and rents. (B) Biceps; fibers are much less atrophic than in quadriceps. Only a few contain vacuoles.

With oxidative enzyme reactions, clusters of diformazan were present in some type I fibers (figure 5A) and these areas stained bright red with a modified trichrome giving the appearance of "ragged red" fibers. Glycogen by periodic acid-Schiff staining usually was abundant in the type I fibers in the form of diffusely distributed punctate granules (figure 5B). Many type I fibers had numerous discrete acid phosphatase positive sites in subsarcolemmal positions with a staining pattern suggestive of lipofuscin (figure 6). Catalase activity by the diaminobenzidine peroxidase method¹⁷ at pH 9.4 was not present.

The type II fibers were of normal size; they had no abnormal lipid accumulation or architectural abnormalities. Their glycogen content appeared normal.

Necrotic fibers were not seen. Intrafusal muscle fibers and intramuscular nerves were not present in the specimens.

In the biopsy from the biceps only about half of the type I fibers showed abnormal lipid accumulations (figures 2B and 3B), but even among these no significantly atrophic fibers were observed (figure 4B). About 50 percent of the type I fibers and all type II fibers appeared unremarkable.

The biopsies of the parents were normal apart from slight type II fiber atrophy in the mother.

Liver. There was some increase of connective tissue around portal areas, where a few chronic inflammatory cells were scattered about. Within the hepatic lobules occasional binucleated cells were seen, with no active necrosis. Hepatocytes contained apparently normal amounts of lipid and glycogen.

Figure 4. Myosin adenosine triphosphatase (ATPase), pH 4.3 preincubation, $\times 436$. (A) Quadriceps, only type I (dark) fibers contain vacuoles. (B) Biceps.

Figure 5. (A) Quadriceps; arrows indicate three atrophic fibers with heavy formazan deposits; reduced diphosphopyridine nucleotide-tetrazolium reductase, $\times 350$. (B) Quadriceps; examples of a type II and type I fiber are marked. The former shows a normal reaction pattern, while the latter exhibit an unusual punctate staining. Periodic acid-Schiff, $\times 350$.

Figure 6. Quadriceps; arrows point to prominent acid phosphatase positive sites (lipofuscin) in three muscle fibers involved in lipid storage. $\times 436$.

Skin. Skin showed no abnormalities. Acinar cells in the sweat glands had unusually abundant lipofuscin. There was no excessive lipid accumulation in these cells.

Electron microscopy. Muscle. Two populations of muscle cells were noted, one normal and one abnormal.

The latter was characterized by the presence of an excess of lipid droplets and by abnormally abundant mitochondrial profiles (figure 7). The mitochondria were often abnormal in shape. Some showed a disproportionate amount of matrix. Paracrystalline inclusions in the intracristal space were found in one muscle cell.

Liver. Hepatic cells showed proliferated smooth-surfaced endoplasmic reticulum (figures 8 and 9). Microbodies appeared numerous. Mitochondria were unremarkable, as were the occasional lipid droplets in hepatic cells. Excessive lipid droplets were seen in a few Kupffer cells.

Chemistry. Carnitine assays in muscle, liver, and plasma of the patient and parents are summarized in table 1. Before carnitine administration the patient's muscle contained only traces of free carnitine; in the plasma and liver it was reduced to about 12 percent of the mean control level. On a high meat and fish diet the plasma carnitine level rose almost $2\frac{1}{2}$ fold. The results of plasma carnitine levels after the oral administration of 500 mg DL carnitine are shown in table 2. There was a steady rise and in 2 hours the plasma level rose to within the low normal range and stayed there for at least 8 hours.

Five months after DL carnitine replacement therapy (2 gm per day) the muscle and liver carnitine levels remained virtually unchanged while the plasma level was now normal. The quantities of some medium-chain urinary

Figure 7. This electron micrograph shows the center of a muscle fiber from the quadriceps. There are numerous abnormally shaped mitochondrial profiles and several large lipid droplets. $\times 14,000$.

Figure 8. This electron micrograph shows part of a hepatic cell. The smooth endoplasmic reticulum is hypertrophied. Glycogen is relatively scanty. Several microbodies are present (arrows). Mitochondria (M) appear normal. $\times 16,000$.

Figure 9. At higher power the membranes of the hypertrophied endoplasmic reticulum can be seen, as well as some glycogen rosettes. $\times 60,000$.

dicarboxylic acids are shown in table 3. Most of them were enormously increased in a random sample of the patient at the height of his muscle weakness. They remained moderately elevated while he was on a ketogenic and high carbohydrate diet, especially on the former. The father showed slightly increased levels of all but adipic and succinic acids. On a random diet, the patient's urine contained 500 mg per gram creatinine of beta hydroxybutyric acid and 74 mg per gram creatinine of parahydroxyphenylacetic acid (high normal values). On a ketogenic diet, however, these levels did not rise significantly.

Results of the forearm metabolic study are summarized in table 4. The significant abnormalities here consisted of impaired utilization of long-chain fatty acids and increased uptake of glucose by forearm tissues. Arterial concentration of C^{14} -oleic acid was $0.26 \mu\text{M}$ per milliliter during the infusion. Arteriovenous differences indicated a net output of $-0.014 \mu\text{M}$ per milliliter while extraction of labeled oleic acid indicated a net uptake of $+0.965 \mu\text{M}$ per milliliter. No C^{14} could be detected either in CO_2 , or in water soluble products over the duration of the infusion and 40 minutes later. Arterial concentration of C^{14} -linoleic acid was $0.094 \mu\text{M}$ per milliliter during infusion. Arteriovenous differences indicated a net uptake of $0.008 \mu\text{M}$ per milliliter while the label extraction indicated an uptake of $0.019 \mu\text{M}$ per milliliter. As with the oleic acid, no evidence of C^{14} was found in CO_2 or in water soluble products in the venous blood during the 20 minute infusion period. (In young adult normal controls 20 to 30 percent of the total C^{14} is recovered in CO_2 under these circumstances).

The activity of gamma butyrobetaine hydroxylase, the enzyme that catalyzes the last step in the hepatic biosynthesis of carnitine, was measured in the patient's liver and in three autopsy control livers. For the patient's liver, 144 pmoles of substrate was converted to carnitine per minute per milligram of protein. The corresponding values in the three controls were 131, 160, and 188 pmoles per minute per milligram of protein.

Carnitine administration. The patient has been receiving 2 gm per day of capsulized DL carnitine in four divided doses taken with flavored milk. No side effects have been encountered. Within a couple of weeks of

Table 1. Carnitine levels

		Plasma (nanomoles/ml)	Muscle (nanomoles/mg noncollagenous protein)	Liver
Patient	A*	7.9	0.50	0.73
	B*	19.4	—	—
	C*	57.0	0.48	1.02
Mother		32.8	13.24	—
Father		33.4	18.35	—
Control†		Mean $\pm$ S.E.M.	51.6 ± 2.48	13.92 ± 0.92
		Range	29.9 to 66.4	7.9 to 22.86
				3.3 to 10.4

*A: On regular diet. B: On high meat and fish diet. C: After 5 months of carnitine administration.
†Muscle controls consist of 20 biopsied non-weak muscles. Liver controls consist of 10 autopsy specimens.

Table 2. Plasma carnitine level after 500 mg DL carnitine loading

	Level (nanomoles/ml)
Fasting	19.4
½ hour	23.3
1 hour	28.0
2 hours	31.8
3 hours	36.7
8 hours	33.8

administration, there appeared to be a steady improvement of exercise tolerance, muscle strength, general well-being, and appetite. At present he has been on this regime for 5 months, with continued improvement of the above parameters. His muscle bulk, however, has only increased slightly to moderately. Significant weakness has remained only in the neck flexors. He has gained 8 lb since the treatment began. His liver presently is not enlarged and his SGOT is now 32 units. The patient has now resumed school full-time, as well as Boy Scout activities and numerous sports.

Table 3. Urinary dicarboxylic acids mg per gram creatinine

	C ₄ succinic	C ₆ adipic	C ₇ pimelic	C _{7:1} heptenedioic	C ₈ suberic	C _{8:1} octenedioic
Patient						
Random sample	—	> 600	120	39	450	320
Ketogenic diet	26.8	47.3	10.0	11.4	29.8	12.3
High carbohydrate diet	23.5	29.0	9.7	8.9	12.9	9.0
Mother						
Random sample	0.5	0	0.9	0.7	0	0
Father						
Random sample	0	2.9	5.0	5.0	5.0	3.8
Normal						
Random sample	4.24	2.6-5	> 2	> 2	> 2	> 2

Table 4. Forearm metabolic study

	Patient		Control† (range)	
	Rest	Exercise	Rest	Exercise
Blood flow ml/min/100 ml displacement of forearm*	9.71	10.33	2-10	5-20
Oxygen consumption μM/min/100 ml displacement of forearm	12.03	16.84	2-12	4-25
Arterial glucose μM/ml	5.6		4-6	
Arteriovenous difference of glucose μM/ml	2.34		0 to 0.4	0 to 0.6
Arterial K+ μM/ml	3.91		3.5 - 4.5	
Arteriovenous difference of K+ μM/ml	-0.11	-0.51	0 to -4	0 to -6
Arterial free fatty acids μM/ml	0.7		0.5 to 1.1	
Arteriovenous difference of fatty acids	-0.129	1.0 to -2.0	2.0 to -2.0	

* Total forearm displacement was 300 ml.
† 20 healthy young adults.

Discussion. Carnitine (γ -trimethylamino- β -hydroxybutyric acid) stimulates the mitochondrial oxidation of long-chain fatty acids in skeletal muscle. L carnitine enables coenzyme A esters of long-chain fatty acids to enter the inner mitochondrial compartment, where they undergo beta oxidation.^{18,19} In vivo forearm study of our patient indicated a severe impairment of the oxidation of oleic and linoleic acids, presumably due to the lack of carnitine in muscle. Skeletal muscle fibers are greatly dependent on fatty acid oxidation for their energy requirements¹² and presumably type I fibers more so than type II. Thus, one of the consequences of muscle carnitine deficiency would be a severe energy deficit, especially in type I fibers. The abundant unutilized long-chain fatty acids apparently can be esterified in the sarcoplasm with glycerol, resulting in copious amounts of triglycerides or neutral fat droplets in the muscle fibers.

The forearm metabolic study in our patient also indicated an increased utilization of glucose by muscle. Undoubtedly this is a compensation for the restricted long-chain fatty acid utilization. In addition, excessive amounts of sarcoplasmic oleic-coenzyme A that may have been present in muscle cells could have caused secondary damage to mitochondrial structures and function.²⁰ Oxidation and peroxidation of excessive long-chain fatty acids could well explain the occurrence of the copious lipofuscin granules in the patient's muscle fibers.

Carnitine occurs naturally in food items, especially in meat and fish. The amounts that are ingested in a normal diet, however, are insufficient to meet the requirements of the entire body.³ Indeed, a biosynthetic pathway for carnitine has been identified in mammals, including man. The following pathway of carnitine synthesis has been more or less established:²¹⁻²³ (1) Lysine $\rightarrow$ (2) 6-trimethyllysine $\rightarrow$ (3) gamma butyrobetaine $\rightarrow$ (4) carnitine. The chemical events in step 1 to 2 and 2 to 3 have not been precisely identified. These steps, however, probably can take place in many tissues, including liver and skeletal and cardiac muscles.³ By contrast, the conversion of gamma butyrobetaine to carnitine takes place mainly, or exclusively, in liver.^{24,25} From this one may infer that carnitine made in liver is then transferred to the blood, from which it is taken up primarily by skeletal and cardiac muscle.²⁶

The cause of carnitine deficiency in our patient could not be identified precisely at this time. The following possibilities may be considered:

1. Failure of carnitine biosynthesis. The normal conversion of gamma butyrobetaine to carnitine *in vitro* by the patient's liver appears to have ruled out a defect in the final step of the biosynthesis. A failure in any of the earlier steps of the biosynthetic pathway, however, would still be possible. In favor of this is the fact that the plasma and liver concentrations were markedly reduced before carnitine administration. On the other hand, a defect in the carnitine biosynthesis by itself could not explain why the concentration of carnitine in muscle and liver did not rise after 5 months of oral carnitine supplements even though a normal plasma level was attained. This finding raises the possibility that the striking clinical improvement (and the apparently improved histochemical features of muscle) was spontaneous and coincidental with, or somehow only indirectly related to, the carnitine administration.

2. Failure of the normal carnitine transport from extracellular fluid into muscle. This could explain the persistently low muscle carnitine level in the face of high plasma levels after carnitine replacement therapy, but would not account for the low plasma (and liver) levels found prior to carnitine supplementation.

3. Failure of "storage-binding" of carnitine in the muscle cells. Although there is no firm evidence that carnitine in skeletal muscle or in other tissues is stored attached to a hypothetical receptor substance, this possibility could explain the low tissue levels and even the beneficial response to oral carnitine supplementation.

4. A primary biosynthetic defect, coupled with a secondary defect in storage or transport capacity, might explain all of our findings. If this were the case, a higher than normal plasma concentration of carnitine might be necessary to provide for the needs of the muscle cell. Additional studies will be required to determine which, if any, of these four possibilities is correct.

The ways in which the liver compensates metabolically for carnitine deficiency deserve comment. The finding of high urinary dicarboxylic acids reflects excessive omega oxidation of long-chain fatty acids.²⁷ Omega oxidation of long-chain fatty acids is not carnitine-dependent and is

believed to take place in the endoplasmic reticulum of liver cells. The marked proliferation of smooth endoplasmic reticulum in hepatocytes seen by electron microscopy in our patient is probably relevant to that. The highest urinary dicarboxylic acid levels were found at the time when the patient was at his worst clinically. After the patient had been receiving a meat and fish diet for some time, and when this diet was enriched with carbohydrates, the urinary dicarboxylic levels dropped, but rose again somewhat on a brief ketogenic diet. This finding is consistent with the expectation that carbohydrates reduced, while excessive fatty acid load augmented, omega oxidation of long-chain fatty acids while their beta oxidation presumably was impaired. The increased number of microbodies (peroxisomes) in liver cells may reflect augmented gluconeogenesis.¹⁷

The clinical picture of carnitine deficiency in the few patients known has been somewhat variable. The degree of skeletal muscle involvement (which was mainly proximal limb, trunk, neck, and facial in distribution) varied from only slight weakness⁵ to severe debility^{1,2,4} or even to a fatal outcome.⁶ It is possible that the cause of carnitine deficiency in different patients may be varied. In all but one⁷ patient thus far known symptoms developed before the age of 20 and in most before the age of 10 years. If carnitine deficiency was present since birth in these patients, we have to assume either that exogenous carnitine had met the metabolic needs of the tissues or that compensatory metabolic pathways had remained sufficient up to a certain period of time.

The intermittency of the liver failure in our patient was of special interest but could not be adequately explained. We believe that the periodic and completely reversible cerebral dysfunction was secondary to the liver failure, but we cannot absolutely rule out a more direct effect of carnitine deficiency on the central nervous system.

The apparent sparing of myocardium in our patient may be explained by the postulation that myocardium will preferentially extract all or most of its required carnitine from the exogenously derived plasma pool. Alternatively, myocardium might be spared because it can efficiently use lactate and ketone bodies as energy sources, which skeletal muscle is unable to do.²⁸

Carnitine deficiency should be suspected in all children or young adults with unexplained mild or severe myopathy and evidence of impaired liver function. The diagnosis also should be suspected when excessive amounts of neutral fat are found in the muscle cells in appropriately stained cryostat sections. It should be emphasized, however, that not all lipid storage myopathies are caused by carnitine deficiency.³ Definite diagnosis depends on the biochemical demonstration of significantly reduced carnitine levels in skeletal muscle. This assay should be done in all suspected cases because at least some forms of carnitine deficiency might be treatable and because the deficiency is a potentially fatal one.

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